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STUDIES ON HEADACHE

Long-Term Observations of the Reactivity of the Cranial Arteries in Subjects with Vascular Headache of the Migraine Type

M. MARTIN TUNIS, M.D.
AND
HAROLD G. WOLFF, M.D.
NEW YORK

DURING migraine headache the painfully involved vessels, conspicuously the temporal artery, are often prominent and tender to palpation.[1] Persons who have frequent, severe vascular headaches may have the temporal artery prominent on one or both sides of the head even when headache-free. Major variability occurs in the size and prominence of the temporal artery from day to day, and indeed from hour to hour. These changes are notable in subjects with migraine headache, as contrasted with subjects who seldom or never have headache. Moreover, persons with migraine headache exhibit such cranial vasomotor changes, especially during periods of frequent headache attacks, and particularly during the 18 to 72 hours prior to the headache. These observations suggest that there is greater variability in the contractile state of the cranial arteries in subjects with migraine than in those who seldom or never have headache. Accordingly, long-term studies were undertaken with improved amplifying and recording instruments to define more precisely these alterations.

METHOD

Glycerine capsules [2] (glycerin-filled rubber spheres in an airtight metal case [3]) were placed bilaterally on the skin over selected cranial arteries to "pick up" the pulsations. Pulse-wave tracings were obtained by connecting the capsule through a piezoelectric pulse-wave attachment to a multiple-channel direct writing recorder.[4] Figure 1 indicates the usual position of the capsule on the cranium. Seventy-five persons subject to migraine headache were studied during various phases of headache and during headache-free periods. Cranial-artery pulse waves were recorded two to five times a week at variable intervals for 5 to 30 weeks. Under these circumstances more than 5,000 records were assembled, representing all phases of the patients' headache state and cranial-artery function, i. e., long before, immediately before, during, and after headache attacks.

From this series, records obtained from the frontal branch of the right temporal artery of 10 migraine subjects at the midpoint of a headache-free interval of not less than two weeks' duration were selected for special analysis.

From the New York Hospital and the Departments of Medicine (Neurology) and Psychiatry, the Cornell University Medical College.

1. Wolff, H. G.: Headache and Other Head Pain, New York, Oxford University Press, 1948.

2. Also called *pelote*.

3. Prepared by the Cambridge Instrument Co.

4. Prepared by the Sanborn Co.

For purposes of comparison, six to eight records were obtained from the frontal branch of the temporal artery at random intervals from 10 subjects who never or seldom had headaches and who did not have headache during the three-month period of study. A total of 72 records were thus obtained. In this nonheadache group the earlier records differed in no way from the tracings taken during subsequent periods of observation.

All the subjects whose records were selected had stable brachial-artery blood pressures (100/70 to 120/80) and pulse rates (70 to 76 a minute). One hundred consecutive pulse waves

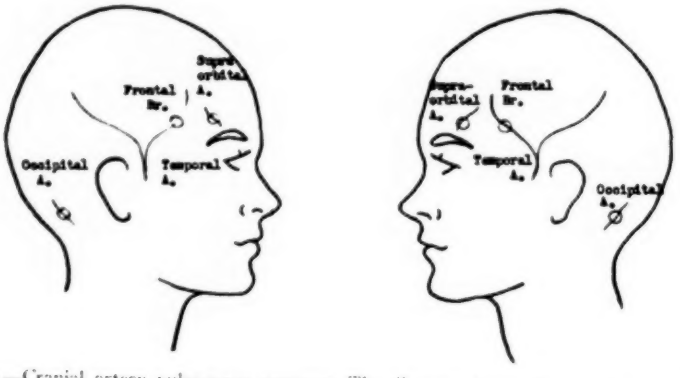

Fig. 1.—Cranial artery pulse-wave contours. The diagram shows the usual position of the capsule for recording.

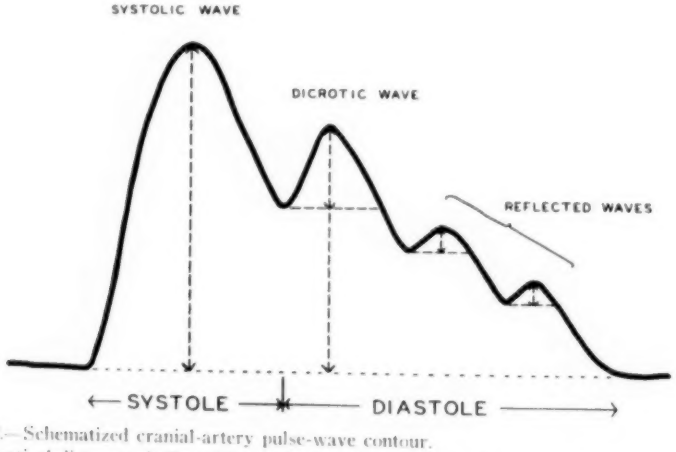

Fig. 2.—Schematized cranial-artery pulse-wave contour.

The vertical distances, indicated by the broken lines and arrows, were measured in millimeters. The total number of reflected waves and their total amplitude also were ascertained for the 100 consecutive pulse waves from the record of each subject.

from the right temporal artery of each subject were measured, and the data from the headache-free migraine group were compared with the data from the nonheadache group.

The components of the cranial-artery pulse wave, as shown in Figure 2, were measured as follows: (1) the height, in millimeters, of the apex of the systolic component from the base line; (2) the height, in millimeters, of the apex of the dicrotic wave from the base line; (3) the height, in millimeters, of the apex of the dicrotic wave from its own base line; (4) the number of the small reflected waves on the diastolic limb of the pulse wave, and (5) the total amplitude of the small reflected waves on the diastolic limb of the pulse wave.

The changes in the amplitude of the arterial pulse wave (systolic apex to base) were taken as evidence of changes in the caliber of the artery. Inferences were drawn concerning the contractile state of the vascular bed under observation, on the basis of these changes, in conjunction with the other measured components of the wave.

RESULTS

Observations.—The data for 1,000 pulse-wave contours of the 10 subjects in each group are shown in the accompanying Table.

*Analysis of Pulse-Wave Contours for Subjects Who Have Vascular Headaches and for Subjects Who Never Have Headaches**

	Headache Subjects		
	During Headache	Free of Headache	Nonheadache Subjects
Systoles			
Wave amplitude			
Range, mm.	17-57	16-48	8-17
Average, mm.	42.7	26.4	12
Standard deviation	± 3.1	± 2.20	± 0.95
Dicrotic, apex to base			
Range, mm.	10-35	6-17	1-12
Average, mm.	18.7	10	6
Standard deviation, mm.	± 3.0	± 2.07	± 0.74
Diastoles			
Dicrotic wave amplitude			
Range, mm.	3.0-29	0.2-7	0-3
Amplitude, mm.	8.1	3.3	1.2
Standard deviation, mm.	± 1.0	± 1.0	± 0.5
No. of reflected waves			
Range	0-4	0-6	0-2
Average	1.4	1.4	0.6
Standard deviation	± 0.82	± 0.82	± 0.53
Size of reflected waves			
Range, mm.	0-16	0.2-2	0.1-1
Average, mm.	1.4	1.4	0.4
Standard deviation, mm.	± 1.3	± 1.31	± 0.4

* Analysis was based on 100 consecutive waves from each of 10 subjects who had vascular headaches (migraine) and 10 subjects who never had headaches.

Each measured component of the pulse-wave contour of the headache-free migraine group was significantly greater than the comparable measurement from the nonheadache group. For example, for the migraine subjects the mean amplitude (systole) was 26.4 mm., as contrasted with a mean of 12 mm. in the nonheadache group.

For the migraine group the average range and standard deviation of the pulse-wave amplitude (systole) were significantly greater than those in the nonheadache group. The amplitude range was 16 to 48 mm., as compared with 8 to 17 mm., and the standard deviation, ± 2.20 mm., as compared with ± 0.95 mm. Also, in the migraine group there was a greater range in the number of reflected waves (0 to 6 versus 0 to 2). The dicrotic-wave amplitude (diastolic) in the migraine group also exceeded the size of this wave in the nonheadache group (3.3 mm. versus 1.2 mm.). The range in size of reflected waves in the headache-free migraine group was 0.2 to 2 mm., with an average of 1.4 mm. (S. D. ± 1.3 mm.), as compared with a range of 0.1 to 1.0 mm., with an average of 0.4 mm. (S. D. ± 0.4 mm.) in the nonheadache group.

Comment: These data indicate that the caliber of the frontal branch of the temporal artery was larger in the headache-free migraine subjects than in the nonheadache subjects. The larger amplitude of the dicrotic wave in the migraine group is additional evidence of increased stretch of the vessel wall, such as might be expected in a vessel of increased caliber.

Further, as compared with the nonheadache group, there was greater variability of the contractile state of the vascular bed under observation in the headache group. This is demonstrated both by the greater range of pulse-wave amplitudes (systole) (16 to 48 mm. versus 8 to 17 mm.) and by the greater range for the number of the reflected waves (diastole) (0 to 6 versus 0 to 2). The range and average size of the reflected waves were also greater in the headache-free migraine subjects.

When compared with the records of the nonheadache group, the records of subjects in the migraine group exhibited greater variability in the contractile state of the studied artery from subject to subject within the group, and indeed from pulse wave to pulse wave on a given tracing from any individual subject.

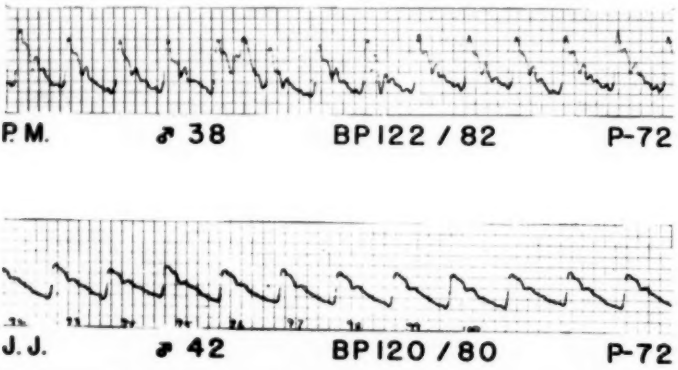

Fig. 3.—Representation right-temporal-artery pulse-wave tracings from a headache-free migraine subject (upper), and a subject who never had migraine (lower).

Note the variability of the pulse waves in the tracing from the migraine subject.

Representative segments of tracings from one subject in each of these two groups are reproduced in Figure 3. Evident are the variability in the pulse-wave contours in the tracing from the headache-free migraine subject and, by contrast, the relative uniformity in the record of a comparable nonheadache subject.

Observations.—The long-term records in the migraine group exhibited a further peculiarity. Three to four days before the onset of headache, the pulse-wave records of the migraine subjects showed a decided increase in the variability of the contractile state of the investigated vascular beds. This variability was sustained until the subject was again in a headache-free phase.

A record of the sequence of contour changes in the temporal-artery pulse waves in a representative subject is reproduced in Figure 4. For 36 to 72 hours before the onset of headache, large pulse waves with a variable contour were recorded. The amplitude generally was well above that exhibited in records from prolonged headache-free phases. Transient facial flushing, often unilateral, and/or alternating pallor were also noted.

Twelve to 36 hours before the headache the pulse-wave amplitude approximated that of the steady state, but there was major variability. Reflected waves, also, were notably more prominent and were increased in total number and size. The incisure was higher on the descending limb than in the wave of the steady state, and the diastolic limb returned more slowly to the base line. The amplitude diminished, and was minimal when the subject reported scotomata in the hour preceding the onset of head pain and indicated increased vascular resistance and vasoconstriction.

Comment: In brief, 100 consecutive right-temporal-artery pulse waves recorded from each of 10 headache-free migraine subjects were analyzed and compared with similar records obtained from 10 subjects who never had headache. The data from these records showed (1) that the caliber of the vessel was significantly larger in the migraine group than in the nonheadache group; (2) that the migraine group

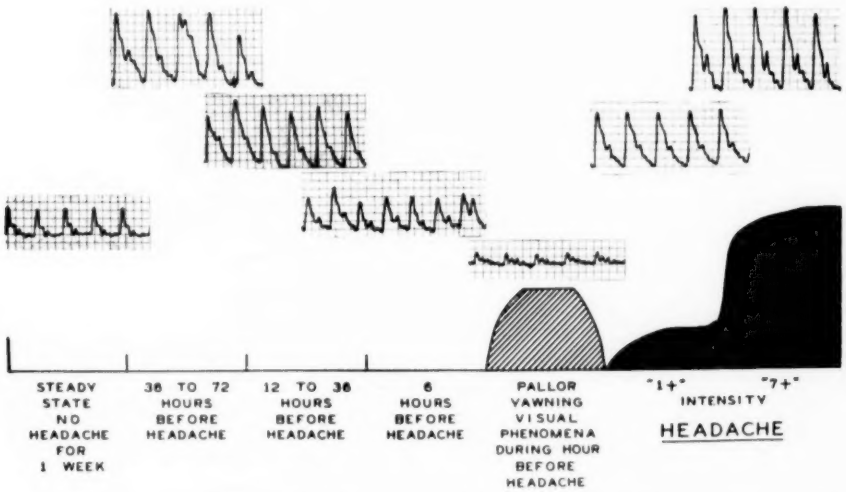

Fig. 4.—Representative record of the sequence of temporal-artery pulse-wave changes prior to and during a headache attack.

Note the variability of the pulse waves in the tracing obtained 72 hours prior to the onset of headache. This variability is sustained until the subject is again headache-free.

exhibited greater variability of the contractile state of the observed vascular bed, and (3) that in the migraine group these characteristics of the temporal-artery pulse-wave records became more conspicuous about 72 hours prior to the onset of the headache.

Observations.—Right-temporal-artery pulse-wave records were obtained during severe headache in 10 subjects during the long-term study of persons subject to migraine headache. One hundred consecutive pulse waves from the record of each subject at the height of the attack were measured, as described above. These data for the 10 subjects were then compared with the data obtained for the same 10 subjects during the headache-free phase. The results are presented in the Table.

The average, the range, and the standard deviation of the systolic pulse-wave and dicrotic-wave amplitudes were greater during headache than were these data when

the same subjects were headache-free. Moreover, shortly after the onset of headache, dilatation was evidenced by the appearance of a concave downward diastolic limb, and a marked reduction in size, and often disappearance, of reflected waves.[5] On tracings obtained later during severe headache, the latter portion of the diastolic limb became distinctly convex upward (Fig. 4), providing an elevated base line and thereby partly obliterating the size and number of the reflected waves. Thus, although the tabulated size and number of the reflected waves approximated the values obtained from records of the headache-free state, the distance from their apex to their base line was greater, and evidenced greater resistance to blood flow.

Comment: The observations indicate that during headache the caliber of the involved vessel is increased, as is its variability. The elevation of the apex of the dicrotic wave from the base line is also increased, and with the other described changes indicates greater stretch on the wall of the involved vessel during headache than in the headache-free state.[5]

The observations indicate that during headache the caliber of the involved vessel is increased, as is its variability. Additional further pulse-wave contour changes including increased size of the dicrotic wave and increased elevation of its apex from the base line, indicate greater stretch on the wall of the involved vessel during headache than in the headache-free state.

It is conceivable that during and preceding headache the magnitude of the changes in function of the involved vascular structures was sufficiently great to produce tissue injury,[6] as indicated by local tissue edema and lowered deep-pain thresholds. The latter have been described elsewhere.[7]

GENERAL COMMENT

Even during headache-free phases, persons subject to migraine exhibited significantly greater variability in the contractile state of particular portions of the cranial vascular tree than did persons who are not subject to headache. Such variability during headache-free phases of persons subject to migraine was especially evident during life periods marred by severe and frequent headache attacks. The striking modifications in cranial-artery function characteristic of the headache attack merely punctuated the more or less continuous series of physiological changes that comprised part of the particular life adjustment of these persons. The observed modifications in cranial-artery function were accompanied by mood alteration, feelings of tension, sustained effort, and restlessness. The concurrence of these changes suggests that these modifications in vascular function and structure are the sequel of sustained adaptive reactions to life stress.[8]

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7. Hardy, J. D.; Wolff, H. G., and Goodell, H.: Pain Sensations and Reactions, Baltimore, Williams & Wilkins Company, 1952.

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SUMMARY

Cranial-artery pulse waves were recorded two to five times a week from 75 migraine subjects. More than 5,000 samples were assembled of cranial-artery pulse-wave tracings taken at various intervals prior to, during, and after migraine headache attacks. Seventy-two cranial-artery pulse-wave records were also obtained from 10 subjects who seldom or never had had headache and who did not have headache during the three months' period of observation.

One hundred consecutive right-temporal-artery pulse waves recorded from each of 10 headache-free migraine subjects were measured and compared with similar records obtained from 10 subjects who never had headache. From the data the following conclusions were drawn:

1. The caliber of the temporal artery was significantly larger in the headache-free migraine group than in the nonheadache group. Also, the caliber during the headache attack was larger than that during the headache-free period, and much larger than that in the nonheadache subjects.

2. The migraine group, as contrasted with the nonheadache group, exhibited greater variability of the contractile state of the observed vascular bed.

3. In the migraine group the characteristic variability of the temporal-artery pulse-wave contours became more striking about 72 hours prior to the onset of headache and was maximal at the height of the headache attack.

4. The pulse-wave contour changes associated with the headache attack merely punctuated a more or less continuous physiological process and may be viewed as part of the life adjustment of these persons.

FACTORS THAT INFLUENCE PROGNOSIS IN ACUTE FOCAL CEREBROVASCULAR LESIONS

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THE TECHNIQUE that utilizes nitrous oxide for the measurement of cerebral blood flow has added much to the knowledge of cerebrovascular physiology. Unfortunately, the new laboratory methods do not give information concerning circulatory differences among diseased, borderline, and normal regions of the brain. The present study has been undertaken in order to correlate some of these new data with clinical experience and to determine some of the clinical elements that influence the prognosis in acute focal cerebrovascular disease.

SCOPE OF STUDY

Clinical observations concerning 223 patients encountered at the Mayo Clinic during a period of two years form the basis of this report. The method for making and recording these observations has been described previously.[1] Cerebral infarction with or without thrombosis was present in 184 (82.5%) of these patients; focal intracerebral hemorrhage was present in 15 (6.7%), and cerebral embolism accompanied by infarction was present in 24 (10.8%). Standard methods were used for the differential diagnosis of these three types of focal intracranial lesions. The accuracy of these clinical diagnoses was confirmed at necropsy in 35 instances. One patient had a clinical diagnosis of focal intracerebral hemorrhage, but necropsy showed that the lesion was massive cerebral infarction. Forty-eight patients received three or more injections of procaine hydrochloride into the stellate ganglion. The first of these injections was performed less than 12 hours after the onset of symptoms in each instance.

RESULTS

The incidence of and deaths from focal cerebrovascular lesions in the entire series are summarized in Table 1. The incidence of and deaths from these lesions according to age in patients who did not receive block of the stellate ganglion are presented in Table 2. Fifty-nine per cent of those having infarcts were 60 years of age or more. The mortality rate in cerebral infarction was much greater in the older age groups than in younger patients. Death occurred in 19% of the patients

From the Sections of Neurology and Psychiatry, the Mayo Clinic.

Read at the Seventy-Eighth Annual Meeting of the American Neurological Association, Atlantic City, N. J., June 15 to 17, 1953.

1. Millikan, C. H.; Lundy, J. S., and Smith, L. A.: Evaluation of Stellate Ganglion Block for Acute Focal Cerebral Infarcts: Preliminary Report of Observations on 87 Patients, J. A. M. A. **151**:438-440 (Feb. 7) 1953.

TABLE 1.—*Mortality Rate in 223 Patients with Focal Cerebrovascular Lesions*

Lesion	Patients	Deaths	
		No.	Per Cent
Infaret	184	28	15
Embolus	24	12	50
Hemorrhage	15	11	73

TABLE 2.—*Incidence and Mortality Rate in 175 Patients with Focal Cerebrovascular Lesions Not Treated with Stellate Block*

Age, Yr.	Infaret		Embolus		Hemorrhage		Total	
	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths
30-39	7	0	4	3	1	1	12	4
40-49	18	1	0	0	0	0	18	1
50-59	33	1	7	3	7	6	47	10
60-69	49	7	4	0	3	2	56	9
70 or more	37	10	1	0	4	2	42	12
Total	144	19	16	6	15	11	175	36

TABLE 3.—*Residuals in 144 Patients with Cerebral Infarct Not Treated with Stellate Block**

Age, Yr.	Total	Normal	Monoparesis, Grade				Hemiparesis, Grade				Died
			1	2	3	4	1	2	3	4	
30-39	7	28	0	0	0	0	14	0	58	0	0
40-49	18	17	0	0	5	0	11	28	17	17	5
50-59	33	15	0	0	3	0	15	13	43	8	3
60-69	49	10	4	2	0	0	16	16	10	27	15
70 or more	37	8	0	0	3	3	6	13	13	27	27

* All figures except "total" are expressed as per cents.

TABLE 4.—*Incidence of Hypertension and Cardiac Disease in 144 Patients with Cerebral Infarct Not Treated with Stellate Block*

Age, Yr.	Total	Hypertension	Cardiac Disease
30-39	7	5	3
40-49	18	12	2
50-59	33	24	5
60-69	49	34	10
70 or more	37	30	14
Total	144 *	105	34

* Some patients had both hypertension and cardiac disease.

TABLE 5.—*Associated Vascular Disease in 144 Patients with Cerebral Infarct Not Treated with Stellate Block*

Age, Yr.	Total	Cardiac Disease				No Hypertension or Cardiac Disease	
		Hypertension	Cardiac Failure	Auricular Fibrillation	Myocardial Infarct	Cases	Per Cent
30-39	7	5	2	1	0	2	28
40-49	18	12	2	0	0	2	11
50-59	33	24	2	2	2	3	9
60-69	49	34	5	0	2	6	12
70 or more	37	30	3	2	1	5	13
Total	144	105	14	5	5	18	13

who were more than 59 years of age, while only 3.6% of those 59 years old or younger succumbed. Deaths from cerebral embolus occurred in younger patients, but deaths from hemorrhage were more frequent in the older age groups.

Table 3 demonstrates the residual motor defects present 14 or more days after the occurrence of cerebral infarction in 144 patients who did not receive stellate block. The percentage of patients having no residual motor defects decreased as age increased, while the percentage of patients with severe damage and the mortality rate increased with increase in age.

Of these 144 patients, 105 (73%) had hypertension and 34 (24%) had clinical or electrocardiographic evidence of cardiac disease, as recorded in Table 4. Table 5 emphasizes the finding that only 18 patients (13%) had neither hypertension nor cardiac disease. The other patients had objective evidence of cardiac disease at the time of physical examination. Table 6 shows the number of patients who did not have stellate block and who became hemiplegic; the length of time from onset of symptoms until development of the maximal physical defect is shown. The patients in each time group who were hemiplegic or dead 14 days later and those who were much improved at the end of the same interval are enumerated. Sixty-nine per cent of the patients in whom hemiplegia developed within six hours or less of onset of symptoms were dead or hemiplegic 14 days later, while death occurred in only 35% of the patients in whom the onset of hemiplegia was slower.

TABLE 6.—*Relation of Speed of Onset of Hemiplegia to Results in Simple Cerebral Infarction, Thrombosis or Embolism in Patients Without Stellate Block*

Speed of Onset, Hr.	No. of Patients	Patients Hemiplegic or Dead 14 Days Later	Patients Much Improved
3	37	33	4
6	39	20	19
12	8	3	5
24	9	3	6

TABLE 7.—*Results of Treatment of Cerebral Infarcts*

	No Stellate Block		Stellate Block	
	Cases	Per Cent	Cases	Per Cent
Infarction				
Total	144	..	40	..
Died	19	13	9	23
Improved	100	69	20	50
Normal	14	10	3	7
Embolism				
Total	16	..	8	..
Died	6	37	6	75

Table 7 summarizes the results in patients who had infarction with or without embolus and who did not receive block of the stellate ganglion, as compared with results in similar patients who underwent this procedure a number of times. The criteria for selection of patients, elements of similarity, and technique of treatment have been reported previously.[1]

COMMENT

It is a well-recognized fact that simple infarction with or without thrombosis is the commonest focal cerebrovascular lesion. Aring and Merritt [2] reported that 81% of their patients had infarction. In our series 82.5% of the patients had simple infarction. The relatively large number of patients in our series (10.8%) who had cerebral embolus is probably explained by the nature of the hospital population in whom these lesions were noted.

The prognosis and the mortality rate in simple cerebral infarction are affected by the age of the patient. Only 8% of all patients 70 years of age or more regained normal function; 40% of them retained severe degrees of hemiparesis or were hemiplegic, while the mortality rate was 27%. Twenty-eight per cent of patients less than 40 years of age regained normal function, and none died. This clinical observation is similar to that of Fazekas and associates,[3] who concluded that the cerebral vessels of arteriosclerotic patients do not respond to increased concentrations of carbon dioxide as well as do those of younger patients. While the residual motor defects were similar in patients in the seventh and eighth decades of life, the mortality rate for patients in the latter group, older by only a decade, was almost twice that in the former.

Only 13% of all patients who had infarction had no evidence of concomitant disease of the cardiovascular system, as judged by such clinical signs as absence of hypertension or detectable cardiac disease. The existence of hypertension or cardiac disease or both appears to be related to the pathogenesis and prognosis of acute focal cerebrovascular lesions. The correlation was even more striking in patients who had embolism; cardiac disease was present in 100% of such patients. The correlation was also striking in patients with hemorrhage; 14 of 15 such patients had blood pressures greater than 200 mm. Hg systolic and 120 mm. Hg diastolic. In general, those patients who had severe hypertension or cardiac disease had more extensive cerebral infarction, as demonstrated by the clinical course.

The pathogenesis of simple cerebral infarction is not clear. The facts that 87% of the patients who had this disease had hypertension or cardiac disease and that the incidence and severity of the lesions increase with age constitute inferential evidence that vasoconstrictive phenomena are not of primary importance in the pathogenesis of simple infarction. Our data reveal that the quantity and extent of infarction became greater in patients in whom vasoconstriction becomes less and less possible anatomically. Bessman, Alman, and Fazekas [4] have demonstrated that acute hypotension in hypertensive patients more than 50 years of age is generally accompanied by symptoms associated with cerebral hypoxia. Two of their patients had reduced cerebral blood flow during an episode of hypotension. The fact that 50 of our 144 patients (35%) experienced onset of cerebral infarction during sleep would make attractive the hypothesis that decrease in blood

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pressure or impairment in venous drainage from the brain is associated with the pathogenesis of cerebral infarction. Specific evidence to support this hypothesis is lacking.

The prognosis of cerebral infarction is affected also by the speed of onset of the symptoms and abnormal physical signs. Of 37 patients in whom hemiplegia developed within three hours after the first symptoms, 33 were hemiplegic or dead two weeks later. On the other hand, almost half the patients in whom hemiplegia appeared after six hours were much improved within two weeks. This observation has been of considerable value in assessing the ultimate outcome in an individual patient fairly early in the course of the disease. It is further confirmation of the concept that the rapid development of cerebral anoxia produces more primary damage than when the depletion of oxygen comes slowly, perhaps partially secondary to edema of tissues.

Block of the stellate ganglion does not appear to exert a favorable effect on the prognosis in cerebral infarction. The mortality rate for 40 patients who received such injections was 23% when embolism was not present. The mortality rate for 144 patients who did not receive stellate block and who had comparable lesions, as well as other physical abnormalities, was 13%. The degree of improvement of the neurologic signs did not differ greatly in these two groups of patients.

The prognosis in acute focal vascular lesions of the brain is affected materially by the nature of the lesions. This is true of the severity of the residual defects, which were least severe in simple infarction and severest in hemorrhage, as well as of the mortality rates, which were 15% in all patients with simple infarction, 50% in those who had infarction caused by embolism and 73% in those who had intracerebral hemorrhage.

Eight patients of the total of 223 experienced one or more convulsions associated with the acute phase of the focal cerebrovascular lesions. The occurrence of these convulsions did not appear to affect the prognosis in any way.

Homonymous hemianopsia was detected and measured in 20 patients. This finding was the abnormal physical sign that oftenest was permanent, without any improvement; 19 of our 20 patients had no improvement in this condition on follow-up examinations. Hemianopsia may have been present in many other patients, but adequate examination could not be conducted in many of them because of alteration in consciousness.

SUMMARY

A study was made of 223 patients who had acute focal cerebrovascular lesions and who were observed at the Mayo Clinic during a period of two years. Of the entire group of patients, 82.5% had cerebral infarction without embolism, 10.8% had cerebral embolism accompanied by infarction, and 6.7% had focal intracerebral hemorrhage.

Factors that influenced the prognosis in these patients were age; existence of hypertension or cardiac disease or both; speed of onset of the symptoms, and whether the lesion was simple infarction, embolism, or hemorrhage.

Injection of procaine into the stellate ganglion did not appear to influence the prognosis.

FAILURE OF ABNORMAL CEREBROSPINAL FLUID PRESSURE TO INFLUENCE CEREBRAL FUNCTION

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THE CLINICAL and experimental association of high cerebrospinal fluid pressures with disorders of the central nervous system has influenced the diagnostic and therapeutic thinking of investigators and clinicians for over half a century. Meyers'[1] critical evaluation of the physiologic experimentation designed to study this relation using experimental animals casts grave doubts on the assumption that there was a necessary association between moderate elevations in pressure and symptomatology. Previously, Browder and Meyers[2] had presented convincing clinical evidence that the orthodox mechanistic thinking in this regard was unsound and unsafe. Nevertheless, studies have since appeared attributing reactions to low pressure[3] as well as to high pressure,[4] and the assumption of a causative relation between high and low pressures and disorders of the central nervous system, at least under certain circumstances, remains widespread among informed experts.

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From the Division of Neurosurgery, Department of Surgery, University of Cincinnati College of Medicine.

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TABLE 1.—*Clinical and Physiological Data on Patients Subjected to Lumbar Barography**

Name	Pro #	Race	Age, Yr.	Sex	St	Addn Diag	Days O	Days Op	Initial Pres P_A Mm. Hg	Initial Pres P_F Mm. H_2O	Fluid Withdrawn Ml.	Fluid Withdrawn P_F	Fluid Added Ml.	Fluid Added P_F	Reactions P_F, Mm. H_2O LPH	AH	R	P	CU
										Contusion									
Guen	150	W	72	F	2	.....	28	..	150/85	50	−20	0	32	500	...	...	...	...	...
Gard	151	W	60	M	2	.....	30	..	105/80	150	−20	−25	50	650	...	...	...	...	...
Klze	152	W	51	F	1	FX	2	..	115/80	25	−24	10	52	500	...	...	...	500	...
Stew	154	N	27	M	1	FX	1	..	115/90	220	−25	80	25	320	80	...	...	250	...
Chen	155	N	38	M	2	FX	2	..	120/75	40	−28	−90	63	350	...	...	...	...	...
John	156	N	62	M	1	.....	1	..	125/75	160	−28	−30	48	550	...	...	...	...	...
Sten	157	W	67	M	1	FX	1	..	115/80	60	−27	−20	47	400	...	...	...	...	...
Walt	158	W	50	M	1	.....	5	..	130/80	160	−20	−10	58	450	...	...	...	...	...
Higg	159	N	25	M	1	.....	2	..	130/75	150	−25	−10	35	550	0	...	...	...	...
Kunk	167	W	19	M	2	.....	6	5	80/55	180	−48	−80	65	550	−20	...	500	...	...
Wolf	171	W	33	M	..	.....	4	..	120/70	200	−50	20	71	600	...	...	...	...	...
Cash	172	W	56	M	1	FX	10	..	.....	300	−50	20	42	800	...	...	...	...	...
Lewi	175	N	17	F	1	.....	3	..	.....	240	−48	20	38	100	...	100	...	...	...
Brad	176	W	63	M	1	CVA	8	..	175/100	140	−60	−150	78	250	...	...	70	...	...
Ervi	177	W	19	M	1	.....	2	..	100/75	90	−30	−60	40	80	...	...	100	...	...
Part	179	W	15	F	1	FX	5	..	100/75	250	−40	−30	45	600	20	...	...	...	...
Roar	180	W	58	M	1	FX	5	..	140/80	130	−40	−120	70	700	...	...	...	...	...
Whit	190	W	29	M	1	FX	5	..	125/65	250	−38	50	43	800	50	600	...	...	...
Cham	194	N	59	M	1	.....	4	..	120/75	160	−35	−40	40	400	...	...	400	...	...
Laws	196	N	47	M	1	FX	1	..	170/100	190	−14	70	24	800	...	...	...	...	...
Brew	201	W	27	M	1	FX	4	..	210/130	400	−80	−110	90	800	...	400	...	...	...
Hute	216	N	33	F	1	.....	6	..	.....	200	−60	−30	68	800	...	...	...	800	...
Kamm	220	W	70	F	1	FX	6	..	150/70	150	−46	−80	58	700	...	...	...	...	...
Cono	223	W	49	M	1	FX	4	..	130/70	100	−50	−60	70	400	...	400	...	...	...
Watk	229	N	56	F	1	FX; CVA	3	..	185/85	80	−23	30	69	400	...	...	400	...	...
Watk	241	..	..	..	1	FX; CVA	32	4	185/130	80	−60	−250	90	800	...	...	...	800	...
Tutt	230	W	35	M	2	FX	15	..	110/80	150	−32	−30	32	750	−30	...	...	...	...
Goll	240	W	63	M	1	.....	6	..	160/95	140	−39	−50	57	550	...	...	...	...	...
Smit	244	N	38	M	1	.....	13	..	.....	270	−60	30	60	600	..	...	...	...	...
Bats	246	N	24	M	1	.....	4	..	150/100	250	−50	−15	56	800	...	...	...	...	...
Mann	247	W	28	M	2	.....	12	..	75/60	140	−50	−20	54	400	...	...	...	...	...
Hugh	248	W	73	M	2	FX; C	4	..	.....	110	−36	−70	46	800	...	800	...	...	...
Shil	249	W	42	M	1	FX	7	..	110/80	250	−40	−60	41	650	...	...	...	...	...
Span	253	W	35	M	1	FX	5	..	.....	40	−12	−20	70	350	...	...	...	...	...
Fowe	255	W	18	M	1	FX	2	..	.....	250	−34	−20	44	900	0	...	...	...	...
Gait	270	W	22	M	2	.....	3	..	.....	60	−19	50	68	300	...	...	...	...	...
Gilb	278	N	26	M	1	.....	2	..	.....	160	−50	−40	59	950	...	...	...	...	...
Pyle	299	N	25	M	1	.....	6	..	115/80	70	−33	−80	75	250	−60	...	...	...	...
Sett	300	N	21	F	1	FX	9	..	.....	275	−50	−70	64	1,100	...	...	...	...	...
Slad	301	N	25	M	2	FX	4	..	.....	325	−29	−120	39	500	...	500	...	...	...
John	304	N	71	M	3	FX	2	..	.....	140	−20	20	67	700	...	...	200	...	...
Malo	307	W	79	M	1	FX	5	..	135/70	50	−50	−80	60	350	...	...	...	...	...
Ash	312	W	37	M	1	.....	8	..	170/100	150	−38	−70	58	350	50	...	...	...	...
Rozl	313	N	51	M	1	.....	15	..	.....	120	−45	−150	55	700	...	...	...	...	...
Hump	329	W	70	M	1	FX	29	..	175/85	125	−57	−100	55	1,000	...	...	...	...	...

Myle	336	N	26	M	1	FX	5	..	140/90	150	−66	−65	53	600	...	600	...	...	...
Ford	349	N	21	F	1	.....	2	..	.....	160	−10	100	39	450	...	...	300	...	...
# 47	Means		42			.....	5	..	134/83	160	−38	−37	54	572	...	...	...	...	...

Diagnostic abbreviations: C, convulsive disorder; CVA, cerebral vascular accident; FX, fracture.

Contusion and Hematoma

Head	164	W	31	M	2	BIS	32	19	.....	60	−50	−150	88	800	−150	...	...	800	...
Samm	185	W	42	M	2	S	28	1	125/80	160	−30	−20	48	700	...	...	...	...	...
Samm	189	..	..	..	2	S	42	13	125/80	150	−60	−50	60	700	...	...	...	...	...
McKi	184	W	48	M	1	BIS; H;	12	3	105/75	180	−60	−40	75	350	...	...	...	...	...
McKi	192	..	..	..	..	FX	30	21	140/75	100	−60	−60	80	750	...	...	...	...	...
Will	186	W	..	M	1	FX; S	2	..	150/100	130	−35	−40	45	500	...	...	...	...	...
Fitz	204	W	57	M	2	S	19	5	125/85	150	−65	−90	67	550	...	...	...	...	...
Fitz	207	..	..	..	2	S	34	20	125/80	90	−50	−50	65	600	...	...	...	...	...
Eldr	206	W	38	M	2	FX; S	0.2	..	.....	200	−20	50	60	1,000	...	1,000	...	...	...
Eldr	209	..	..	..	2	FX; S	13	5	145/90	450	−54	−130	54	1,100	...	...	...	...	...
Coop	212	W	50	M	3	FX; S; I	4	1	155/100	350	−78	−170	73	1,300	...	...	...	...	1,100
Wolf	224	W	51	M	1	FX; S	10	10	115/70	140	−48	−70	53	650	0	...	...	...	...
Smit	227	W	51	M	2	S; I	19	13	120/75	150	−25	−20	42	1,100	...	...	800	...	...
Holt	231	W	24	M	2	H	61	45	.....	60	−39	−80	39	140	−60	...	...	...	...
Dunn	260	W	30	M	1	FX; I	8	..	110/85	50	−36	−150	73	1,000	...	...	...	...	...
Fitz	321	W	61	M	1	FX; S	5	..	115/65	180	−39	−40	41	400	−40	400	...	...	...
Fitz	330	..	..	..	..	FX; S	22	..	135/75	110	−66	−140	74	400	...	...	...	...	...
# 17	Means		44			.....	19	12	128/81	159	−48	−73	61	708	...	...	...	...	...

Diagnostic abbreviations: BIS, bilateral subdural hematomas; FX, fracture; H, subdural hydroma; I, intracranial hematoma; S, subdural hematoma.

Miscellaneous Head Injuries

Gull	162	W	31	M	1	CYST	700	..	110/75	80	−60	−200	86	600	−100	400	...	...	...
McCo	173	W	35	M	1	FX; CON	3	..	.....	80	−40	5	38	300	...	...	...	...	...
Jone	174	N	38	F	1	FX; CON	2	..	160/70	100	−50	−80	66	350	−40	...	...	...	...
Camp	214	N	30	M	1	CON	2	..	135/75	120	−50	−50	69	400	...	...	...	...	...
Star	232	W	49	M	2	FX	6	..	150/75	350	−60	−70	60	600	...	...	400	...	...
Rect	235	W	47	M	1	ATR	..	..	110/75	170	−50	−130	65	800	...	...	...	...	...
Eatm	251	N	65	M	2	FX	7	..	100/65	110	−54	−180	72	700	−180	...	...	...	...
Hard	282	W	54	M	1	FX; CON	3	..	.....	200	−50	−20	78	900	20	...	...	...	...
Smar	284	N	34	F	1	CON	3	3	.....	250	−66	30	34	500	...	...	...	...	...
Henn	328	W	79	M	3	GUNS; C	3	3	95/45	230	−75	−150	77	700	...	...	...	...	...
Bush	343	N	32	M	1	FX	4	4	120/70	200	−78	−20	67	460	...	...	...	...	...
# 11	Means		45			.....	3	3	122/69	172	−58	−79	66	574	...	...	...	...	...

Diagnostic abbreviations: ATR, atrophy; C, convulsive disorder; CON, concussion; CYST, post-traumatic cyst; FX, skull fracture; GUNS, gunshot wound.

Cerebral Thrombosis

Spru	160	W	80	M	3	.....	..	..	175/85	160	−30	−70	42	550	...	...	...	...	...
Spru	161	..	..	..	3	.....	..	..	160/90	130	−18	0	26	400	...	...	...	...	...
Mase	169	W	65	M	1	.....	70	..	135/70	150	−48	−100	72	800	−20	...	500	...	...
Moor	218	N	41	M	1	HCVD	..	..	120/75	85	−50	−20	70	400	...	...	...	...	...
Unwi	221	W	56	M	1	HEM	11	..	170/80	150	−50	−40	50	400	−40	...	...	200	...
Camp	222	N	43	M	3	.....	8	..	170/100	300	−45	−20	48	800	(0)	...	...	(800)	...
Eggl	236	W	63	F	2	.....	20	..	.....	180	−22	40	50	600	...	...	...	...	...
Mill	238	W	52	M	1	.....	360	..	150/90	170	−75	−170	99	700	...	...	...	...	...
Andr	257	N	67	F	2	SYPH	7	..	240/140	175	−46	−80	69	800	...	...	...	...	...
Bott	263	W	47	F	1	.....	3	..	140/80	180	−40	−30	50	900	20	500	...	...	...

TABLE 1.—*Clinical and Physiological Data on Patients Subjected to Lumbar Barography**—Continued

Name	Pro #	Race	Age, Yr.	Sex	St	Addn Diag	Days		Initial Pres		Fluid Withdrawn		Fluid Added		Reactions Pf, Mm. H_2O				
							O	Op	P_A Mm. Hg	Pf. Mm. H_2O	Ml.	Pf	Ml.	Pf	LPH	AH	R	P	CU
Cerebral Thrombosis—Continued																			
King	266	W	74	F	1	EMB; CA	..	..	120/60	110	—38	—70	66	1,000	0	...	...	...	...
Robe	271	W	70	F	3	.....	4	..	195/130	150	—59	—100	72	860	...	...	...	...	...
Lock	275	N	63	F	2	DIAB	10	..	175/165	120	—30	—40	50	700	—40	...	500	...	...
Meck	281	W	59	M	1	.....	340	..	175/100	150	—53	—50	64	900	...	...	...	...	...
Meck	286	..	..	..	1	.....	350	..	150/85	140	—42	—70	72	700	...	...	...	...	...
Mack	285	N	48	F	1	.....	13	..	250/160	275	—27	60	87	750	60	...	...	...	...
Mite	287	N	43	F	1	.....	17	..	.....	250	—46	—30	52	700	...	...	...	...	...
Webb	317	W	52	F	2	HCVD	3	..	250/130	175	—42	0	68	700	20	...	700	...	...
Smit	323	N	60	F	1	.....	..	..	165/80	150	—48	—140	64	900	—140	...	...	...	...
Blev	324	N	57	F	1	HEM	4	..	150/75	80	—24	—80	43	300	...	...	300	...	...
Brow	325	W	78	M	2	HCVD	4	..	115/65	80	—55	—100	75	800	...	...	...	...	...
# 21	Means		60			.....	10	..	169/95	158	—40	—57	59	688	...	...	...	...	...

Diagnostic abbreviations: CA, carcinoma; DIAB, diabetes; EMB, intracranial embolus; HEM, intracranial hemorrhage; HCVD, hypertensive cardiovascular disease; SYPH, meningovascular syphilis.

Hypertensive Encephalopathy

Jack	254	N	62	M	3	.....	7	..	130/105	300	—50	—70	70	1,500	...	...	...	...	1,200
Murp	258	N	42	F	1	.....	5	..	200/150	220	—38	—20	46	900	—20	900	...	...	...
Murp	262	..	..	..	1	.....	13	..	250/170	300	—45	—70	56	1,000	—70	...	...	...	...
Murp	279	..	..	..	1	.....	41	..	.....	160	—60	—90	78	1,500	...	1,500	...	...	...
Murp	319	..	..	..	3	.....	8	..	.....	200	—48	—150	51	750	...	...	...	...	...
Bing	267	W	48	F	2	.....	2	..	.....	170	—29	20	59	800	...	...	700	...	...
Bing	273	..	..	..	2	.....	9	..	.....	150	—25	—50	39	600	...	...	...	...	...
Bogg	288	N	49	M	1	.....	60	..	255/100	450	—29	75	32	850	...	...	...	...	...
Wirt	295	W	53	M	1	CVA	180	..	150/95	200	—48	—60	57	700	0	...	...	...	...
Gran	297	N	40	F	1	C	10	..	.....	250	—57	—20	58	850	75	...	250	...	...
High	309	N	44	F	1	.....	7	..	.....	150	—42	—60	53	400	—60	...	...	...	...
Well	318	W	57	M	2	.....	90	..	220/110	450	—45	45	55	800	...	...	...	...	...
Most	322	N	58	M	1	CVA	9	..	135/75	90	—25	—15	44	750	...	...	...	...	...
Most	337	..	..	..	1	CVA	32	..	125/75	220	—30	—10	32	340	...	...	...	...	...
Hirs	327	W	51	M	1	CA	9	..	.....	200	—60	—120	65	650	...	...	...	...	...
Harr	335	N	44	M	1	.....	..	..	200/85	230	—50	—10	46	500	...	...	200	...	...
# 16	Means		50			.....	9	..	196/107	234	—43	—38	53	806	...	...	...	...	...

Diagnostic abbreviations: C, convulsive disorder; CA, carcinoma; CVA, cerebrovascular accident.

Intracranial Neoplasm

Goeb	188	W	46	M	1	GLIO	9	2	105/75	150	—91	—50	111	600	...	...	...	...	...
Goeb	198	..	..	..	1	GLIO	10	3	.....	80	—60	—80	78	600	...	...	...	...	...
Suth	242	W	55	M	2	GLIO	3	..	150/50	450	—22	0	47	900	...	...	...	...	...
Suth	243	..	..	..	2	GLIO	3	..	.....	145	—36	20	38	800	...	...	...	...	...
Todd	245	W	42	M	2	ASTR	..	8	160/90	420	—32	80	34	1,000	...	1,000	...	...	...
Morg	252	W	38	F	1	MEN	3	..	.....	150	—60	—95	76	400	...	...	...	...	...
Gooc	261	N	41	M	1	MEN	24	..	130/90	50	—7	40	27	350	...	...	350	...	...
Cost	264	W	58	M	2	GLIO	2	..	125/75	110	—39	—60	60	900	...	...	...	...	...
Bull	269	N	65	M	1	PIT	72	..	92/54	150	—60	—30	79	800	...	...	...	...	...

Carr	208	N	26	F	1	CRAN	2	..	125/90	375	−37	0	42	950	30	...	...	...	...
Ness	308	W	59	M	2	GLIO	2	1	105/70	800	−62	−120	64	1,400	...	...	...	...	1,000
Ness	315	..	..	..	2	GLIO	3	1	100/65	375	−70	−120	76	1,400	...	...	...	...	1,000
Σ 12	Means		48			.....	3	2	121/73	271	−48	−35	61	841	...	...	...	...	...

Diagnostic abbreviations: ASTR, astrocytoma; CRAN, craniopharyngioma; GLIO, glioma; MEN, meningioma; PIT, pituitary adenoma.

Miscellaneous Organic Diseases of the Central Nervous System

Nich	187	N	43	F	1	ANEU	17	..	210/100	150	−35	3120	35	400	...	...	...	400	...
Kell	191	N	46	F	1	SYPH	..	..	190/120	150	−40	−70	52	400	−40	...	...	...	...
Kell	195	..	..	..	1	SYPH	..	..	.....	160	−40	−40	45	500	...	...	...	160	...
Tayl	193	W	21	M	3	ABSC	..	..	125/65	160	−55	−40	65	600	...	...	...	...	...
Tayl	197	..	..	..	2	ABSC	..	..	.....	170	−75	10	15	20	10	...	...	...	...
Adam	213	W	59	M	1	ATR	..	..	180/100	150	−60	−80	70	900	...	...	...	...	...
Gerh	239	W	41	M	2	ATR	1,500	..	.....	85	−50	−40	90	600	...	...	...	600	...
Youn	250	N	38	F	1	.....	..	..	.....	200	−36	−60	60	800	...	...	...	...	...
Kram	283	W	69	M	1	.....	30	..	150/75	200	−40	−140	49	700	...	...	...	...	...
East	296	W	76	M	1	AS	..	..	175/75	120	−70	−250	90	900	−250	...	...	...	...
Coul	302	N	35	F	1	ANEU	60	..	.....	160	−58	−220	68	800	...	...	300	...	...
Dean	303	W	44	M	1	BUER	40	..	150/90	130	−63	−110	86	650	...	...	...	...	...
Dean	314	..	..	..	1	BUER	60	..	150/85	180	−80	−60	80	680	...	...	...	...	...
Core	316	W	74	M	2	AS	30	..	135/75	100	−58	−140	82	550	...	...	550	...	...
Jack	333	N	85	M	1	.....	..	..	170/95	140	−38	−80	59	1,000	−80	...	...	...	...
Jord	340	N	46	F	1	ANEU	5	..	.....	275	−52	−45	60	240	...	...	250	...	...
Lemo	344	N	73	M	2	AS	4	..	175/85	110	−27	−200	67	350	−180	...	80	...	...
Σ 17	Means		54			.....	30	..	165/88	155	−52	−85	64	593	...	...	...	...	...

Diagnostic abbreviations: ABSC, cerebral abscess; AS, cerebral arteriosclerosis; ANEU, intracranial aneurysm; ATR, cerebral atrophy; BUER, cerebral Buerger's disease; SYPH, meningovascular syphilis.

Controls

Byrn	181	W	29	M	1	LAC	1	..	115/75	120	−50	−60	65	400	...	...	...	400	...
Shie	183	W	28	M	1	MIG	..	..	125/75	140	−51	−60	80	500	−30	...	250	...	...
Ryde	199	W	38	M	1	None	..	..	110/75	150	−80	−170	88	650	−80	...	...	...	...
Ryde	200	..	..	..	1	None	..	..	.....	165	−60	−50	90	80	60	...	...	80	...
Duti	205	W	47	M	1	CON	3	..	155/85	100	−42	−10	62	500	...	...	...	500	...
Horn	256	W	28	M	1	FX; LAC	3	..	125/70	200	−41	−30	70	700	...	...	700	...	...
Appl	272	N	33	M	1	FX; LAC	1	1	.....	180	−50	−160	68	1,000	...	...	250	...	...
Rose	277	W	38	M	1	LAC	3	3	105/70	150	−47	−70	60	700	...	...	...	...	...
Goet	292	W	52	M	1	CAO	..	..	.....	160	−48	0	64	650	...	...	...	...	...
Robe	293	W	57	M	1	DEF	..	..	125/80	150	−40	−80	17	600	...	...	...	...	...
Brow	305	N	39	M	1	SCH	180	..	.....	200	−49	−30	51	850	...	...	...	...	...
Must	310	W	50	M	1	FX	3	1	180/100	160	−37	0	44	600	...	...	600	...	...
Rade	329	W	27	M	1	LAC	5	..	140/80	250	−54	−20	55	800	0	...	...	...	...
Σ 13	Means		39			.....	3	1	131/79	163	−50	−57	63	618	...	...	...	...	...

Diagnostic abbreviations: CAO, oral carcinoma; CON, concussion; DEF, congenital deformity of cervical spine; FX, skull fracture; LAC, laceration; MIG, migraine; SCH, schizophrenia.

* Addn Diag indicates additional diagnoses; AH, "atypical" headache; CU, "Cushing's reaction"; Initial Pres, initial pressure; LPH, "lumbar puncture" headache; Means, the arithmetical mean with the exception of days after onset, where it refers to the geometric mean; Ml., milliliters of fluid added to or withdrawn from cerebrospinal space; Mm., millimeters of arterial or cerebrospinal fluid pressure; O, onset (days after); Op, operation (days after); P, pain; P_A, arterial pressure; P_V, cerebrospinal fluid pressure; Pro Σ, procedure number; R, "restlessness"; St, status (1, oriented; 2, confused; 3, comatose); Σ, number of patients studied.

We have measured and recorded the cerebrospinal fluid pressure from a number of locations in several hundred patients with and without abnormal pressures and disorders of the central nervous system and have noted their response to procedures that modified the pressure. The extent of the induced deviations in pressure is greater than that of any that have previously been recorded in the literature. Certain of these observations and the inferences to be drawn from them are reported here.

SAMPLING CONSIDERATIONS AND TECHNICAL METHODS

The patients were adult men and women, both white and Negro, from the neurosurgical, neurological, and medical services of a large general hospital. The patients from the neurosurgical service were unselected except that patients with shock, unusual restlessness, a recent neurosurgical exploration, or urgently indicated surgical treatment were not usually studied. Otherwise, all the patients admitted during the period from June 1951, to April, 1953, were studied unless the investigative team was busy with other patients or there was no clinical indication for a lumbar puncture. An operative permit was obtained in all cases and the nature of the procedure briefly explained to the conscious persons. After preliminary exploratory studies of the methods and its limitations were made, advanced age, irreversible illness, elevated cerebrospinal fluid pressure, coma, convulsions, focal neurological signs, clinical evidence of brain swelling or a space-occupying intracranial lesion, recent intracranial hemorrhage, skull fracture, and craniectomies older than one week were not considered contraindications, with two exceptions. Patients with cerebrospinal fluid fistulas did not have the fluid pressure lowered below the ambient, and the patients with fistulas and skull defects had the pressures only moderately elevated. The patients from the neurological and medical services were selected because of our interest in the condition from which they were suffering. No patients were given sedation for the study. It was most unusual not to be able to study a patient because of his restlessness, although restless subjects gave information of more limited value because their activity so frequently modified the pressures. The usual reason for the failure of a study was the technical inability to insert a needle into the desired vessel or the lumbar subarachnoid fluid space and to record the pressures free of artifact as fluid was added and withdrawn. It should not be inferred from our favorable experience with these subjects that the indiscriminate performance of lumbar punctures on all patients is innocuous.

Fluid was added to and withdrawn from the cerebrospinal fluid spaces in these several hundred patients with and without disorders of the central nervous system in order to study the relation between the fluid pressure and changes in craniospinal blood volume.[5] The technique of measuring and recording continuously the fluid and vascular pressures was described in that report. One hundred fifty-seven of these patients had what will be termed a "lumbar barography" performed under essentially the same conditions. With the patient lying on his side, fluid was first withdrawn from the lumbar subarachnoid fluid space, reinjected, and then enough withdrawn to return the pressure to the original level. The internal jugular venous pressure, the internal carotid or brachial arterial pressure, and usually the respirations were also recorded throughout the procedure.

OBSERVATIONS

Certain of the pertinent clinical and physiological data are listed in Table 1. In Table 2 the subjects are classified arbitrarily according to whether the initial pressure was elevated above 200 mm. of water when referred to the level of the needle in the spine, was depressed below 100 mm. of water, or was between these limits. Each group in this Table was subclassified according to whether the disorder was traumatic in origin or was due to some other cause. A few patients who did not have any disorder of the central nervous system or who had apparently

5. Ryder, H. W.; Espey, F. F.; Kimbell, F. D.; Penka, E. J.; Rosenauer, A., Podlosky, B., and Evans, J. P.: Mechanism of the Change in Cerebrospinal Fluid Pressure Following an Induced Change in Volume of the Fluid Space, J. Lab. & Clin. Med. **41**:428-435, 1953.

recovered from their disease are also listed. The mean pressure to which the fluid was lowered and then raised in each group is listed; it required the withdrawal of 45 ml. and the addition of 60 ml., on the average, to induce these pressure changes. Also recorded are the number of the principal reactions associated with the procedure and the mean fluid pressure at which these reactions were induced.

Most of the patients had no symptomatic or physiological reactions to the lumbar barography. If they had neurological symptoms or signs, the procedure did not modify them. If a cardiac dysrhythmia or tachycardia, an abnormal blood pressure, or a respiratory disorder was present, the procedure did not change it (Fig. 1A-D). In the absence of a reaction there was no objective or subjective change in the patient's condition. Occasionally a patient fell asleep during the procedure, but usually the initial discomfort of introducing the needles, the necessity of lying for an hour or two in a rather restricted position, and the anxiety associated with an unusual experience kept him awake. Not infrequently the jugular venous pressure fell as much as 50 to 100 mm. when fluid was withdrawn and returned to its initial level when the fluid was added. This was the only consistent change in any modality.

TABLE 2.—*Incidence of Immediate Reactions to Fluid Withdrawal and Addition*

			Mean Pressure, Pf, Mm. H_2O			Headache		"Jitters"		"Atypical" Headache		"Cushing" Reaction	
	Group*	No.	Initial	Lowest	Highest	Pf	No.	Pf	No.	Pf	No.	Pf	No.
I	A	18	300	—40	720	35	6	600	2	365	3	950	2
	B	17	350	—15	875	0	4	235	3	950	2	1,065	3
II	A	46	150	—50	620	—20	11	400	8	600	6	...	..
	B	44	155	—75	690	—55	14	525	10	800	3	...	..
	C	8	160	—60	570	—20	3	475	2	...	..	...	..
III	A	17	60	—75	480	—90	4	100	1	...	..	...	..
	B	7	70	—65	580	....	..	465	3	...	..	...	..
	Total	157	175	—55	660	—30	42	440	29	640	14	1,020	5
						25%		18%		9%		3%	

* Groups are designated as A, patients with trauma; B, patients with other organic disease of the central nervous system; C, patients recovered.

REACTIONS

Headaches.—A supraorbital and suboccipital "drawing" headache was induced in 25% of patients, at an average pressure of —30 mm. of water. This headache will be referred to as a "lumbar puncture" headache because of its clinical characteristics. The remaining patients did not complain of such a headache, even though their average pressure was reduced to —53 mm., and occasionally to as low as —250, of water. In the group of conscious patients who could complain of this symptom, it appeared without regard to their initial pressure or the condition from which they were suffering. Occasionally patients in coma who would respond to painful stimuli behaved at low pressures as though they were suffering from such a stimulus. The incidence of such behavior in these patients was no greater than the incidence of headache in the others.

In 15 patients the lumbar barography was performed before and after a cuff was applied around the neck, with the cuff inflated to an average pressure of 560 mm. of water. Table 3 gives the incidence of headache and the average pressure at which it occurred under these two conditions.

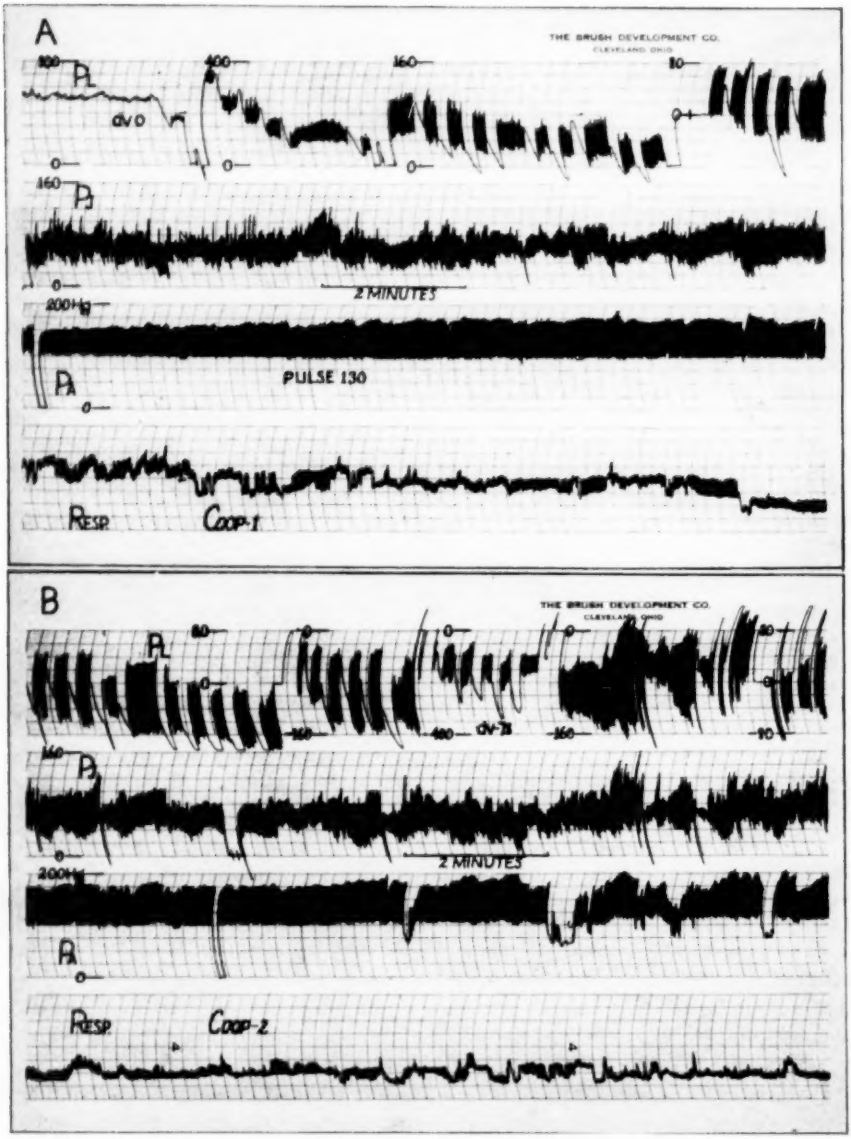
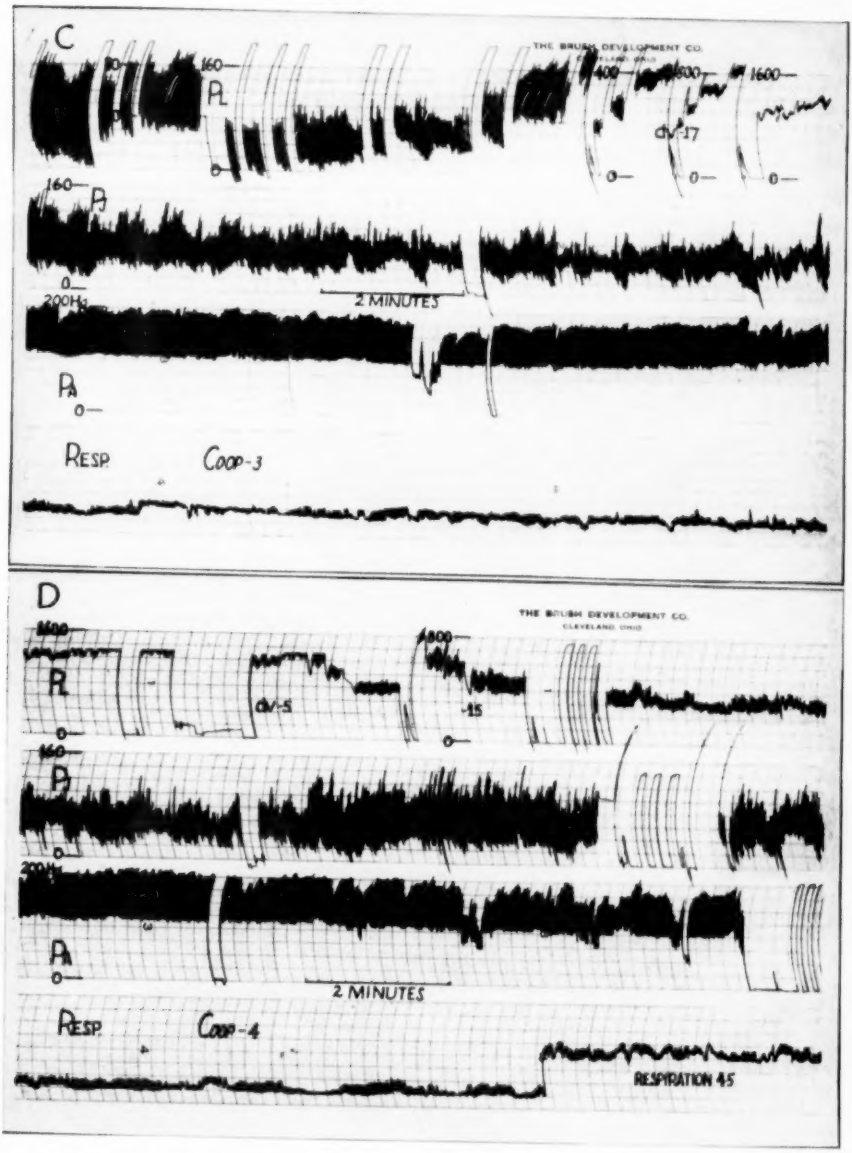


Fig. 1.—Failure of lumbar barography to modify pathological vital signs.

The comatose patient was studied 24 hours after the operative removal of a traumatic acute subdural hematoma and an intracerebral hematoma. He died 24 hours after the barographic procedure. The lumbar subarachnoid fluid pressure (P_L), the internal jugular venous pressure (P_J), the internal carotid arterial pressure (P_A), and the respirations (*RESP*) are recorded. The fluid and venous pressures are in millimeters of water. Calibration of the gauges is shown in D. As fluid is added to or withdrawn from the subarachnoid fluid space, the recorded pressure, P_L, is not that in the lumbar space. This artifact identifies the periods of fluid addition

(Legend continued on next page)



or withdrawal. Cumulative changes in volume, dV, are indicated. Intermittently the gauges recording the fluid and vascular pressures are referred to the reference pressure, zero. As the attenuation of the gauges and the level of the reference pressure (the right atrium) were changed, these were indicated. The respirations (*RESP*) indicate the qualitative changes in pressure in a Frank capsule strapped to the chest.

The gradual slow swings in arterial pressure, from 150 systolic and 100 diastolic to 210 systolic and 115 diastolic, also occurred in a previous portion of the tracing before barography. The sudden drops in arterial pressure are considered to be artifacts but may represent periods of ventricular standstill.

Nine per cent of the patients complained of headache when the pressure was increased. This headache is termed "atypical," because in location and description it was unlike the "lumbar puncture" headache. Nine of the 15 patients with this headache had a skull fracture or skull defect, and the pain was usually localized to the involved area. Such headaches became more intense as the pressure was elevated and were relieved by lowering the pressure. In the six remaining patients no apparent "reason" for the headache was found.

TABLE 3.—*Effect of Neck Cuff on Incidence of Headache**

Procedure	Cuff, P_C	Lumbar Fluid, P_F	Internal Jugular, P_J	After Fluid Withdrawal, P_F	Headache at P_F	Proportion with Headache	
						$P_F = 45$	$P_F = -75$
No cuff	0	180	135	−75	0	0/15	2/15
Cuff	560	400	425	45	145	8/15	....

* The mean pressures are in millimeters of water.

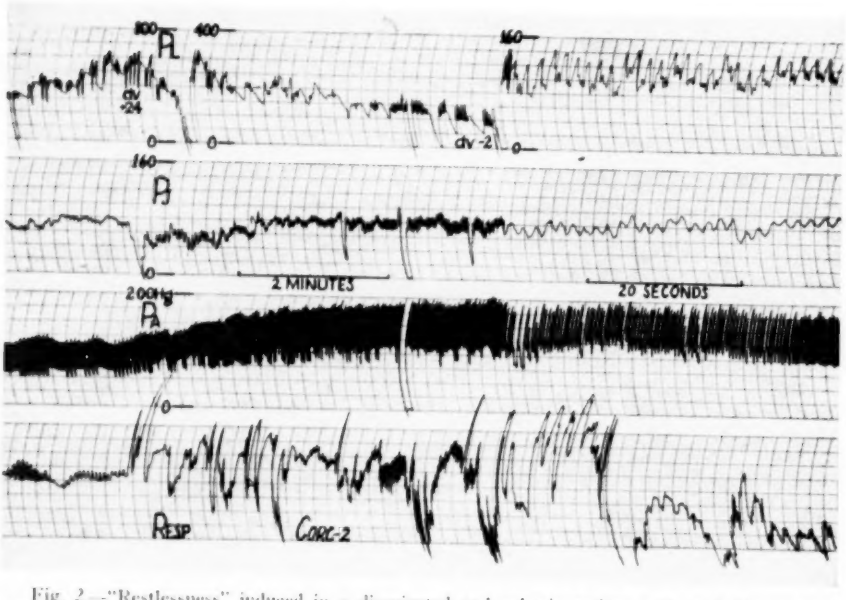


Fig. 2.—"Restlessness" induced in a disoriented and aphasic patient with probable cerebral thrombosis.

The "jitters" reaction interrupted the performance of a lumbar barographic examination, which up to that time had not been associated with any change in physical signs. The symbols are similar to those in Figure 1.

"Restlessness."—A characteristic reaction occurred in 18% of the patients, without regard to the condition from which they were suffering. In conscious patients the reaction was preceded by the complaint of pain in the back or perineum or down the legs. It began only on the addition of fluid. It was commoner if there had been technical difficulty in getting a free fluid exchange between the needle and the lumbar subarachnoid fluid space. It could usually be aborted by not adding more fluid at this time, or made worse by adding fluid more rapidly or in large

amounts. This characteristic reaction when fully developed consisted of restlessness, anxiety, evidence of considerable discomfort in the back, moaning and groaning, and tossing about. Usually the patient perspired and felt chilly, sometimes having a shaking chill. The respirations became irregular, rapid, and deep. If the patient was confused before the procedure, he became more so during this reaction, and often had to be restrained. The blood pressure invariably increased, as did the jugular venous pressure (Fig. 2). The cerebrospinal fluid pressure did not change much, except for the irregular respiratory pulses. If the fluid pressure was above the initial pressure at the time the reaction occurred, it fell toward the

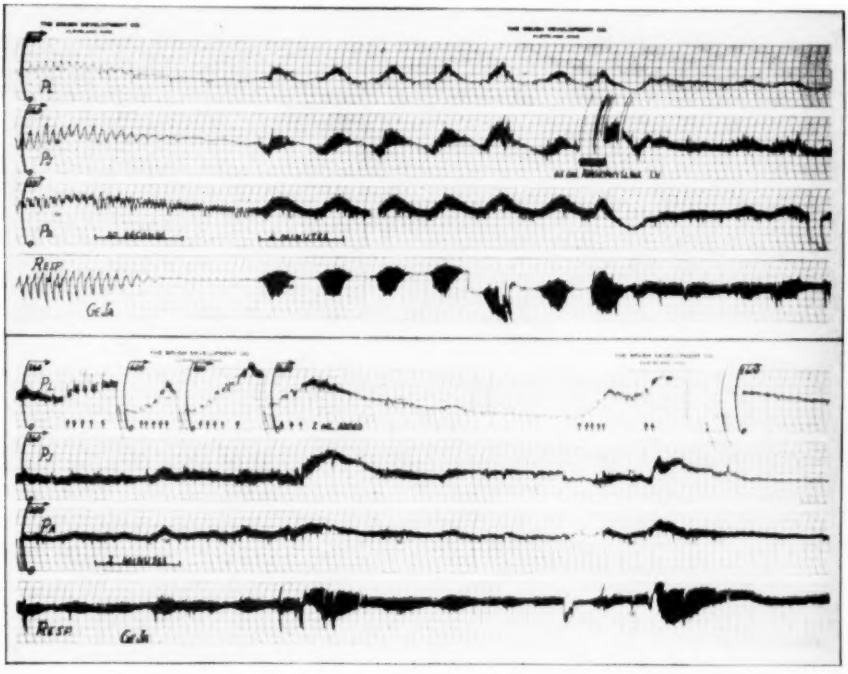


Fig. 3.—Induction of the "Cushing phenomenon."

The pressure tracings are those of a comatose patient with hypertensive encephalopathy. The Cheyne-Stokes respirations and the characteristic associated changes in fluid and vascular pressures were largely suppressed by the administration of aminophylline. The addition of fluid was followed twice by hypertension, tachypnea, and elevation in internal jugular venous pressure. Note that the induced hypertension is no greater than that occurring spontaneously with the Cheyne-Stokes respiration. The symbols are similar to those in Figure 1.

equilibrium pressure, just as it did in the absence of a reaction. Withdrawal of fluid did not abort it. It subsided in from 10 to 60 minutes, depending on its severity.

Restlessness occurred without regard to the patient's condition or state of consciousness. Occasionally it appeared after the fluid was withdrawn and then returned, but before the pressure returned to its initial level, although its incidence was greater in patients whose pressure was kept elevated for longer periods than usual, as in the group in which the pressure-volume curve was obtained while the cuff

was around the neck (Table 3). In 6 of 15 patients the reaction developed with the cuff around the neck, and in none did it develop during the control study.

"Cushing Phenomenon."—The fluid pressure was not usually elevated to near the mean systolic pressure, for at the start of this investigation there was no a priori suggestion that this was innocuous; clinical tradition suggested, rather, the reverse.[6] Furthermore, the direct purpose of this study was to determine the parameters of the pressure-volume curve; data obtained at pressures of more than a few hundred millimeters above the point of inflection of the curve are not valid for this purpose. In patients whose initial pressure was normal, the induction of pressures

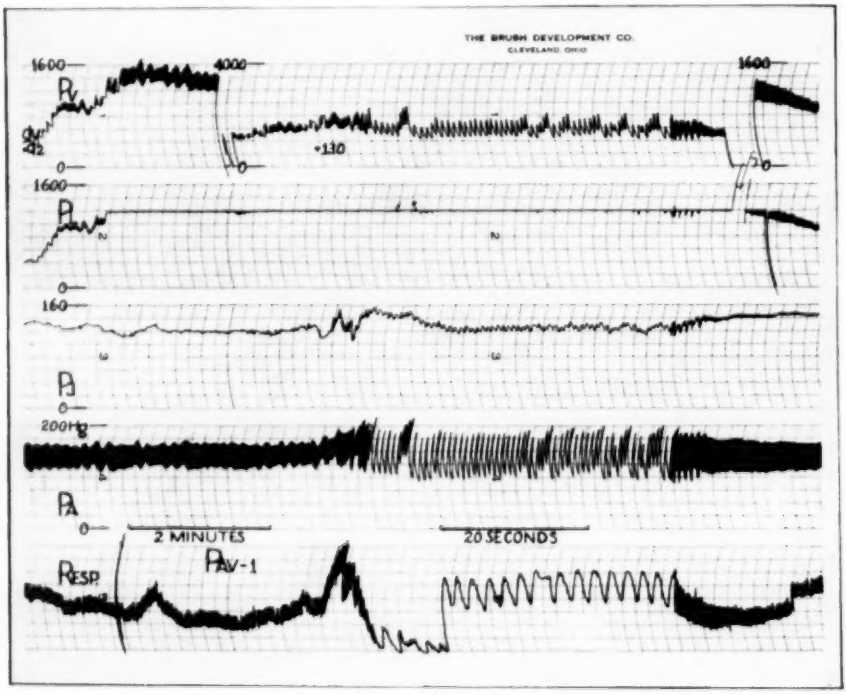


Fig. 4.—"Cushing phenomenon" with associated bradycardia.

Portion of the ventricular barograph of a patient still in deep coma and hyperventilating 38 days after an automobile accident and the removal of an acute subdural hematoma. The limits of the gauge recording the lumbar pressure were exceeded at 1,200 mm. The pulse irregularity at the height of the "Cushing reaction" was due to a series of ventricular ectopic beats. At the height of the reaction the tracing was run 6.25 times faster. The symbols are similar to those in Figure 1.

above 600 to 800 mm. of water required the addition of considerable fluid, since it was absorbed so rapidly.[5] The more fluid was added under high pressure, the more commonly were the prodromata of the "restlessness" reaction induced, and the appearance of these symptoms was considered a contraindication to the further

6. Cushing, H.: The Blood-Pressure Reaction of Acute Cerebral Compression, Illustrated by Cases of Intracranial Hemorrhage, Am. J. M. Sc. **125**:1017-1044, 1903.

addition of fluid. Many of the patients had operative defects or a fractured skull which led to pain as the pressures were elevated, another contraindication to the further addition of fluid. In the few patients in whom the pressure was elevated to the mean arterial blood pressure, the blood pressure rose, the respirations became deeper and faster, and the jugular pressure rose (Fig. 3). Bradycardia occurred in only one patient (Fig. 4) and apnea in none; the reaction differed in these respects from that which Cushing observed in dogs [7] or from that which is seen in monkeys after the extradural or intracerebral injection of oil.[8]

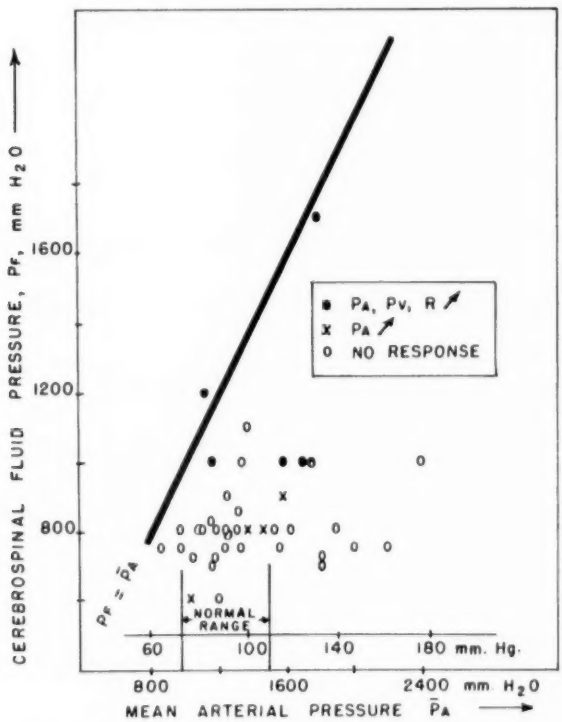


Fig. 5.—Relation between fluid and vascular pressures and induced hypertension.

The fluid and mean arterial pressures (the diastolic pressure plus one-third the pulse pressure) of all subjects whose pressure was elevated above 600 mm. by adding fluid to the cerebrospinal fluid space are plotted. Pressures for the five patients who became hypertensive with an increase in jugular pressure (P_V) and in the rate and depth of respiration (R) are indicated, as well as those for the four in whom hypertension developed without changes in jugular venous pressure or respiration. The diagonal line indicates equality of the fluid and mean arterial pressures.

7. Cushing, H.: Concerning a Definite Regulating Mechanism of the Vasomotor Center Which Controls Blood Pressure During Cerebral Compression, Bull. Johns Hopkins Hosp. **12**:290-292, 1901.

8. Ryder, H. W.; Espey, F. F.; Kristoff, F. V., and Evans, J. P.: Observations on the Interrelationships of Intracranial Pressure and Cerebral Blood Flow, J. Neurosurg. **8**:46-58, 1951.

In Figure 5 the highest fluid pressure obtained in all patients with induced pressures about 600 mm. is plotted against the mean blood pressure at that fluid pressure, except that in those patients in whom hypertension appeared at high pressure the fluid pressure at its time of appearance was plotted. Since hypertension, tachycardia, and hyperventilation also characterize the "restlessness" reaction, this

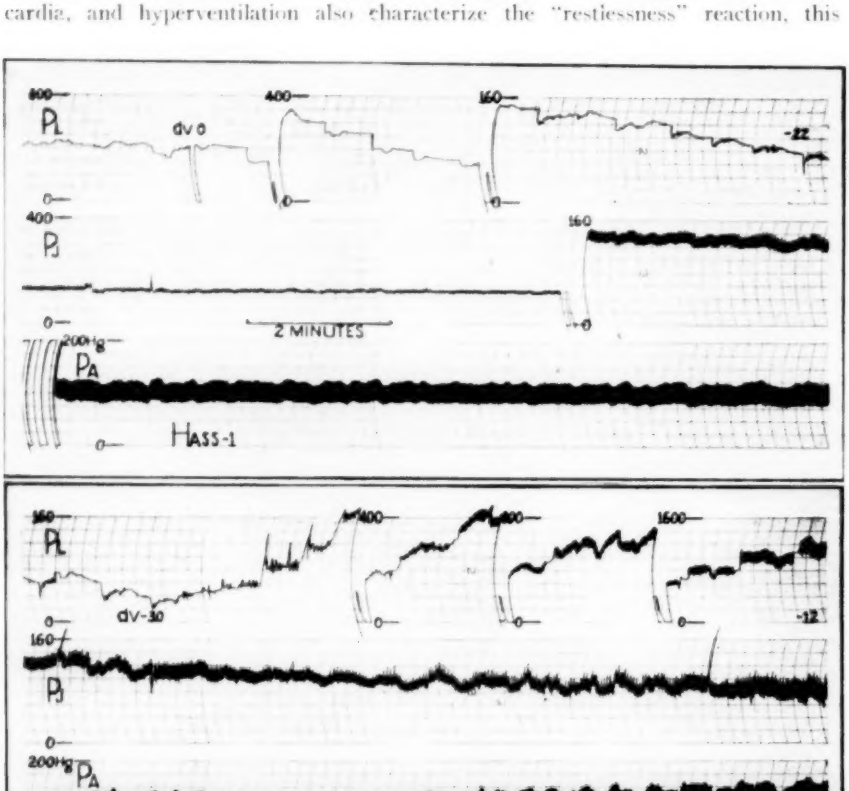


Fig. 6.—Effect of intracerebral hemorrhage induced by lumbar barography. See report of Case 1 in text. The symbols are similar to those in Figure 1.

response could not be distinguished with certainty from the "Cushing phenomenon" in comatose patients, who could not complain of the prodromata of "restlessness." In several of the patients moderate hypertension without other objective symptoms occurred before this limiting pressure was recorded. Occasionally this was associated with an "atypical" headache. This isolated hypertension was commoner in patients whose blood pressure was labile, in that it went up and down during the study without reference to the fluid pressure. Occasionally the blood pressure increased to an equal degree with such painful stimuli as the "lumbar puncture" headache.

Other Reactions.—Certain reactions were characteristically absent, notably nausea, vomiting, shock, and apnea, a feature which distinguishes lumbar barography from encephalography and ventriculography.

The reaction of one patient suggested that further bleeding was induced by the procedure (Case 1, Fig. 6). One patient (Case 2), who displayed no unusual reaction during the study, died an hour and a half after being returned to the ward. A convulsion occurred at the end of one study (Case 3, Fig. 7).

Figure 6 continued.

COMMENT

The procedure has induced changes in fluid pressure beyond the limits of the equilibrium pressures that occur in health and disease. Symptoms and signs, if present, were not modified except by the imposition of one or more of four distinct reactions. It remains to be proved that these reactions were not due directly to the changes in fluid pressure.

Reactions Associated with Lumbar Barography.—The commonest reaction, "lumbar puncture" headache, appeared in 25% of the subjects when the pressure

was lowered. At a given pressure, its incidence was significantly higher when the identical procedure was performed with a cuff around the neck (Table 3). The mean pressure at which the reaction occurred with the neck cuff inflated was also significantly higher. The stress that induced the headache was therefore not the low pressure itself; inferentially, it was due to a factor modified by the relation between the fluid pressure and the intracranial venous pressure, as Kunkle, Ray, and Wolff [9] have deduced from extensive experimentation.

The "atypical" headache usually occurred only in patients with a skull defect. In those patients it is reasonable to infer it was due to distortion of local struc-

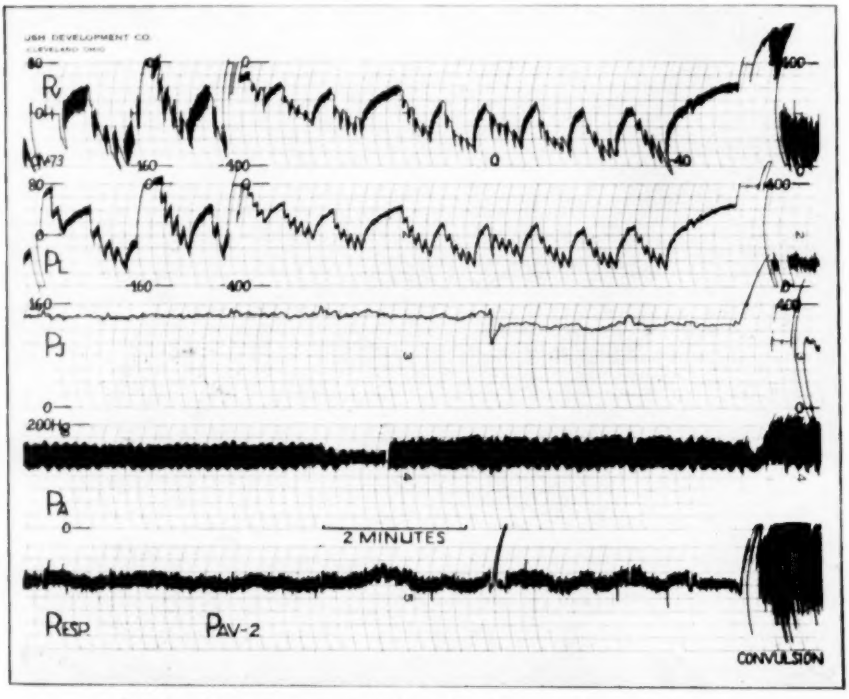


Fig. 7.—Onset of status epilepticus following ventricular barography.

The tracing is a later portion of the study illustrated also in Figure 4. No discrepancy in the fluid pressures was induced by withdrawing ventricular fluid and lowering the fluid pressure to —350 mm. After the last withdrawal, the pressures were allowed to return toward the equilibrium pressure, and the patient had a Jacksonian seizure. See text, Case 3. The symbols are similar to those in Figure 1.

tures at the site of the defect. In the other six men the headache was moderate in intensity. This low incidence as an induced phenomenon, the inconstant relation of the headache to specific disorders, and its failure to become incapacitating suggest that it was not caused directly by the high pressures at which it was

9. Kunkle, C. E.; Ray, B. S., and Wolff, H. G.: Experimental Studies on Headache: Analysis of the Headache Associated with Changes in Intracranial Pressure, Arch. Neurol. & Psychiat. **49**:323-358, 1943.

observed. In many of the subjects studied headaches were characteristic of their disorder.

"Restlessness" was observed in 18% of the procedures. In Table 1 this reaction is bracketed with "pain." The "pain" is not considered further in this analysis, although it is thought to be a prodrome of "restlessness," for most of the patients who exhibited "restlessness" also had this "pain" in the back or perineum or down the legs. This "restlessness" is clinically identical with the reaction which Schega[9b] and Bresgen [10] reported after the addition of fluid to the epidural space at the third and fourth thoracic vertebrae. They attributed it to the associated rise in subarachnoid fluid pressure. The evidence that leads to our inference that the reaction is not due to the pressure changes associated with the procedure is multifold: The reaction occurs in relatively few patients, so that it is not a necessary concomitant of high pressures; the pressures at which it is observed are widely variant, it being induced occasionally at pressures less than the initial pressure; in men in whom it occurs it does not constantly recur at the same pressure when the procedure is repeated; it occurs only on the addition of fluid; it is preceded by a symptomatology suggestive of nerve root irritation, which is not a necessary concomitant of high fluid pressures; it can be aborted by failure to add more fluid when the prodromata appear; it is a function of the rate and amount of fluid addition; its incidence is higher when the communication between the subarachnoid space and the spinal needle is not free and, after it has developed, its course is not modified by lowering the fluid pressure.[11]

It would be pertinent to our problem to prove whether the "Cushing phenomenon" is a function of an increase in pressure alone or of a relation between the mean intracranial arterial pressure and the fluid pressure, much as the "lumbar puncture" headache is due to a relation between the intracranial venous pressure and the fluid pressure, and is not a function of the fluid pressure alone. No other investigators have considered that this reaction may be a function of pressure alone, since the hypothesis that it is induced in some way by a factor related to a diminution in cerebral blood flow is intuitively accepted. The problem is complicated further by one's difficulty in distinguishing this reaction from hypertension without related phenomena and from the hypertension associated with the "restlessness" reaction, and by the absence of the bradycardia and apnea which Cushing considered so characteristic in dogs.[6] In fact, the only features this reaction usually has in common with that observed by Cushing are that hypertension occurs and that the fluid pressure is near the mean arterial blood pressure. The incidence of the Cushing phenomenon in our series is too small to permit one to determine whether the absolute pressure reached or a critical difference in fluid and arterial pressures is the factor initiating the pressor response. However, since pressures far higher than those seen clinically in disorders characterized by high fluid pressures were induced usually without initiating this reaction, the inference is valid that this pressor phenomenon is not mediated directly by pressures much higher than those usually seen in patients with grave disorders of the central nervous system which are characterized by high pressure.

10. Bresgen, C.: Über seltene Zwischenfälle bei der epiduralen Novocaininjektion, Klin. Wchnschr. **27**:571-575, 1949.

11. Rosenauer, A.; Ryder, H. W.; Penka, E. J.; Espey, F. F., and Evans, J. P.: Über eine Hochdruck-Reaktion bei lumbaler Barographie, to be published.

Reactions Not Associated with Lumbar Barography.—Certain reactions may occur with other procedures that otherwise have aspects in common with lumbar barography. A consideration of the factors common to all three procedures gives insight into the variables responsible for the reactions.

Von Storch [12] reported the fluid pressure responses to encephalography. The immediate reactions to the two procedures are notably different. The addition of the first 10 ml. of air invariably caused headache in those of his subjects who were not anesthetized, a reaction we have not seen on introducing fluid initially. It may be inferred that the induction of a volume change in the cerebrospinal fluid space is not alone sufficient to cause the headache.

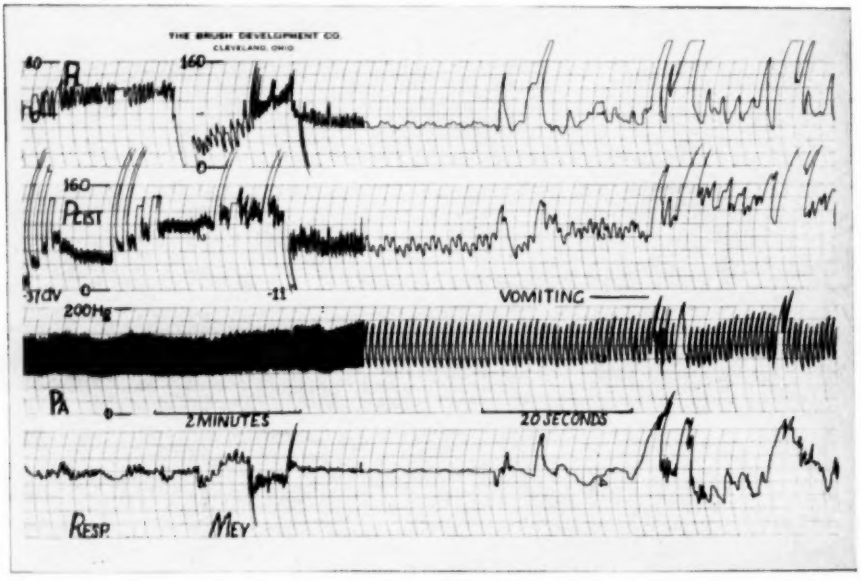


Fig. 8.—Appearance of nausea and vomiting following lateral cisternal barography. The patient was hemiplegic following thrombosis of the left middle cerebral artery. *Pcist* refers to the pressure in the lateral recess of the basal cistern. The abrupt deviations in the recorded pressures reflect the intrathoracic and intra-abdominal pressure changes that are associated with vomiting. The symbols are similar to those in Figure 1.

Nausea and vomiting do not occur in association with lumbar barography. When fluid is added to and withdrawn from locations other than the lumbar subarachnoid fluid space, nausea and vomiting may occur. These reactions followed the addition of fluid to the lateral cistern in a patient in whom this space was entered inadvertently by way of the jugular foramen (Fig. 8). They were also observed on several occasions after ventricular barography, and it is well known that they may complicate ventriculography. Since encephalography is performed with the patient sitting, and the other procedures with the patient recumbent, we may infer at least

12. Von Storch, T. J. C.: Clinical Application of the Craniovertebral Dynamics to Encephalography, Brain **59**:250-271, 1936.

that the posture of the patient does not account in itself for the difference in incidence of the nausea and vomiting that may complicate these various procedures.

Vasomotor collapse occasionally follows encephalography and ventriculography. It has not been observed after lumbar barography, even though the arterial pressure has been monitored continuously. The induction of vasomotor collapse, also, is not a function of posture alone.

In ventriculography and encephalography fluid and air are interchanged without inducing an appreciable net change in the volume of the cerebrospinal fluid spaces. In lumbar, lateral cisternal, and ventricular barography successive increments of fluid are added or withdrawn until large deviations in pressure from the original pressure are induced. Because of this difference in techniques, it may be inferred that the extremes in pressure recorded with lumbar barography are greater than those that occur with encephalography or ventriculography, even though the pressures are not recorded routinely with the latter procedures. Von Storch [12] recorded them in his series; they were much less than those we have induced with lumbar barography. Therefore the difference in incidences of immediate headache, nausea, vomiting, and vasomotor collapse in the three procedures is not due to the induction of high or low pressures alone.

Lumbar and ventricular barography induce the same change in cerebrospinal fluid pressure for a given amount of fluid added or withdrawn, no matter where the fluid is added or withdrawn (Fig. 9*A* and *B*), and in our experience an appreciable discrepancy in pressures in the lumbar and ventricular spaces rarely occurs. On the occasions on which it has been seen, it has not induced symptoms. Two inferences follow: First, each procedure had the same effect on the volume of the craniospinal vascular bed.[5] Second, the difference in incidences of nausea, vomiting, and vasomotor collapse is due neither to a change in the volume of the craniospinal vascular bed nor to a discrepancy in the fluid pressures anywhere in the cerebrospinal fluid spaces.

In summary, we may infer that the factors that lead to the immediate headache characteristic of encephalography, the vasomotor collapse that may occur with encephalography and ventriculography, and the nausea and vomiting that may complicate encephalography, ventriculography, and lateral cisternal or ventricular baroraphy are not any one of the following factors acting alone or the result of their interaction: high or low fluid pressure, discrepancy in fluid pressure in different parts of the cerebrospinal fluid system, distention or compression of the craniospinal vascular bed, posture, sedation, or anesthesia.

Symptoms Associated with Other Factors Modifying the Fluid Pressure.—There are a number of other factors that may modify the fluid pressure, sometimes to an extreme degree. The fluid pressure, in patients with a high initial pressure, may be doubled by the voluntary ingestion of 1.5 liters of water, without inducing symptoms.[13] Hyperventilation and the administration of carbon dioxide, amyl nitrite, and arterenol (Nor-epinephrine) all cause characteristic changes in fluid pressure and symptoms characteristic of the drug administered or the procedure performed, rather than any symptom complex characteristic of the induced and

13. Ryder, H. W.; Espey, F. F.; Kimbell, F. D.; Penka, E. J.; Rosenauer, A.; Podolsky, B., and Evans, J. P.: The Mechanism of the Effect of Changes in Blood Osmotic Pressure on the Cerebrospinal Fluid Pressure, J. Lab. & Clin. Med. **41**:543-549, 1953.

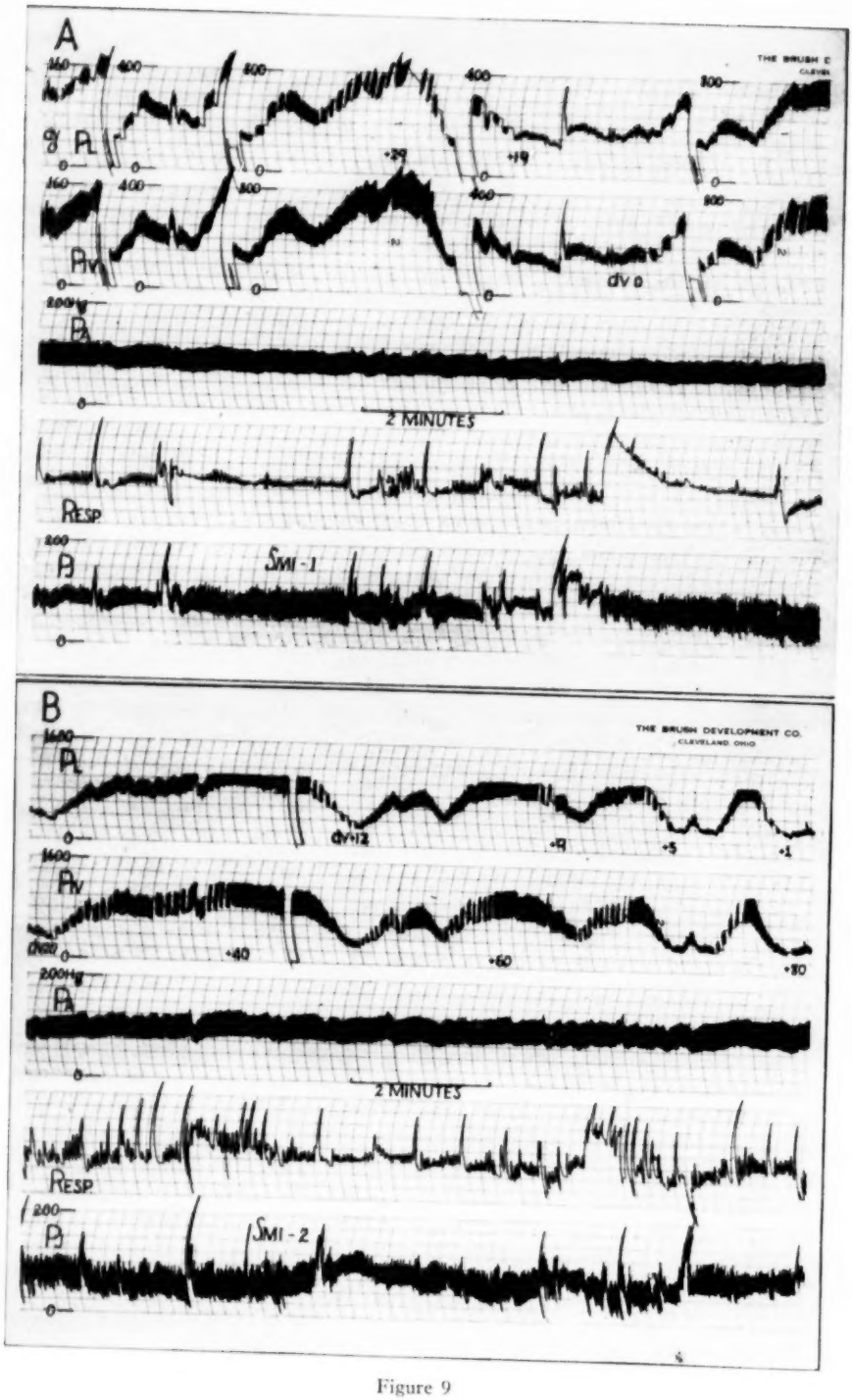

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Figure 9

associated change in pressure.[14] Modifications of the intrathoracic pressure may induce transient changes in fluid pressure of 1,000 mm. of water, without inducing symptoms.[15] The application of pressure to a cuff around the neck causes dramatic suffusion of the face and symptoms referred to the eyes and face, which may be explained as due to the stimulation of peripheral end-receptors. It raises the fluid and jugular venous pressures (Table 3), but does not induce headache or symptoms or signs of a central nervous system disorder or modify such symptoms and signs if they are present, except for the "lumbar puncture" headache. The symptoms associated with these specific procedures are not due, therefore, to the accompanying changes in fluid pressure.

Cause of Symptoms Associated with Deviations in Pressure.—We have inferred that, since the fluid pressure of itself, as well as several other modalities, has no direct effect on cerebral function, there are no absolute pressure receptors in the human brain. The problem remains as to what factor, so frequently associated with changes in fluid pressure, does modify cerebral function. The commonest reaction to lumbar barography, "lumbar puncture" headache, is associated inferentially with dilation of the intracranial venous bed. The distention of the great veins as they enter the sinuses causes this pain. The "atypical" headache can usually be explained by the mechanical displacement of recently injured tissues at the site of a fracture line or the distortion of dural structures at the site of a skull defect. The effect is induced by the elevation of intracranial pressure, but the necessary condition for pain is the skull defect. The "restlessness" appears to be induced by some factor related to the accumulation of fluid in the subdural or epidural spaces near the site of the injection of fluid. Since the necessary condition is the sudden accumulation of an abnormal volume of fluid, the causative factor is related to the distortion or displacement of neural structures, rather than the pressure change in the subarachnoid fluid space which is so frequently associated with this distortion. The initial headache that invariably characterizes encephalography appears to be related to the displacement of fluid in the posterior fossa by air. Inferentially, the mechanism of this headache, which occurs without an appreciable modification of pressure, is

14. Ryder, H. W.; Espey, F. F.; Kimbell, F. D.; Penka, E. J.; Rosenauer, A.; Podolsky, B., and Evans, J. P.: Influence of Changes in Cerebral Blood Flow on the Cerebrospinal Fluid Pressure, A. M. A. Arch. Neurol. & Psychiat. **68**:165-169, 1952.

15. Ryder, H. W.; Espey, F. F.; Kimbell, F. D.; Penka, E. J.; Rosenauer, A.; Podolsky, B., and Evans, J. P.: Effect of Changes in Systemic Venous Pressure on Cerebrospinal Fluid Pressure, A. M. A. Arch. Neurol. & Psychiat. **68**:175-179, 1952.

EXPLANATION OF FIGURE 9

Fig. 9.—Correspondence of fluid pressures on addition of fluid to or withdrawal from either the ventricular or the lumbar fluid spaces.

The lumbar and ventricular barography was done in a case of a post-traumatic convulsive disorder that had led to a basal skull fracture and rhinorrhea. The latter had ceased before the barographic procedure. The pressures in a lateral ventricle (P_{IV}) and the lumbar subarachnoid fluid space (P_L) are both recorded from catheters in the appropriate locations. The addition of fluid to either the ventricle or the lumbar space and its withdrawal from the lumbar space induced no discrepancy in the fluid pressure or changes in the vital signs. Twenty minutes later, after withdrawal of fluid from the ventricle to a pressure of — 100 mm., and the addition of fluid to return it to the original pressure of 120 mm., the patient vomited. The flattening of P_L at pressures above 1,100 mm. in B is due to the gauge limits having been exceeded. The symbols are similar to those in Figure 1.

related to the removal of fluid of essentially the same specific gravity as the brain, which forces the contents of the posterior fossa to shift under the influence of gravity, pulling on pain-sensitive supporting structures.[9] The nausea and vomiting seen frequently after ventriculography, encephalography, or an induced change in the volume of a lateral recess are not seen after lumbar barography, although usually no discrepancy in the pressures in any of the cerebrospinal fluid spaces occurs with any of the procedures and the pressure changes induced by lumbar barography are far greater than those associated with ventriculography or encephalography. We have inferred from the absence of discrepancies in pressure that all the procedures have the same effect on the volume of the craniospinal venous bed, a change which is not therefore the cause of the symptoms. In the case of encephalography the reactions are related inferentially to the displacement of the brain and the stretching of its supporting structures associated with the removal of fluid and its replacement by air. With ventriculography, presumably distortion of or traction on neural structures induced by the change in size of the ventricle is the source of the reflex stimulus. After the addition of fluid to and its withdrawal from a lateral recess, distortion of nearby structures presumably induces the symptoms.

From these several inferences the general induction follows that the stimulation of afferent fibres by stretch or distortion is the factor that induces the symptoms associated with changes in cerebrospinal fluid pressure, on the occasions when symptoms follow the particular procedures discussed.

Summary.—It is common knowledge that many procedures and conditions that cause symptoms and signs of central nervous system disturbance are associated with abnormal fluid pressures. It is not generally appreciated that these procedures and conditions are not necessarily so associated. Other investigators have observed that many procedures and conditions that modify the fluid pressure do not cause symptoms and signs of central nervous system disturbances, and that certain signs and symptoms of abnormality are not remitted necessarily by a return of the pressure to normal. We have generalized and extended the basis for these inferences and have shown inferentially that the induction of reactions associated with extreme deviations in fluid pressure was in no case due directly to the induced change in pressure. The common factor in these acute reactions is related to the stretching, distortion, or translation of craniospinal structures.

CONCLUSIONS

Acutely abnormal cerebrospinal fluid pressures do not interfere with cerebral function. There can be no syndrome specific for either high or low intracranial pressure.

Afferent fibers in the human central nervous system which are sensitive to absolute pressure do not exist. When symptoms or signs of cerebral dysfunction are associated with a change in cerebrospinal fluid pressure or an abnormal fluid pressure, the association results from the effect of a factor or factors common to both the pressure and the dysfunction, and not from a causative relation between pressure and dysfunction.

Certain factors which modify the cerebrospinal fluid pressure may also modify cerebral function by stretching or displacing cerebral tissues. This stretching or displacement may occur at any cerebrospinal fluid pressure.

There is no valid physiological basis for two clinical inferences: First, fluid pressures within the range of normal indicate either the absence of or the correction of a grave disorder of the central nervous system; second, the proper treatment of conditions associated with an abnormal fluid pressure consists in returning the pressure to normal.

REPORT OF CASES

CASE 1.—R. H., a white man aged 49, was brought to the receiving ward after being struck by a trolley-bus. He was unresponsive and was bleeding from the nose and mouth. For 10 minutes after admission he had extensor spasms of all extremities, followed by relaxation and seizures on the right side. There was a compound fracture of the anterior aspect of the frontal bone on the left, with a large periorbital hematoma and left exophthalmos. In the operating room, the left frontal bone was debrided, and bilateral temporal burr holes were made. The brain was swollen and tense bilaterally. A small amount of clotted blood was removed from the subdural space on the right. Needles were placed in both lateral ventricles, and grossly bloody fluid was found. A portion of the temporal lobe was sucked away on each side. The patient was returned to the ward unresponsive, with the pupils pinpoint. A tracheotomy had been done, and the airway was maintained clear.

The following morning, with the patient in the same clinical status, a lumbar barography was done. The initial lumbar fluid pressure was 450 mm. of water. The grossly bloody fluid contained 2,200,000 erythrocytes per cubic millimeter. After the withdrawal of 30 ml. of fluid, the pressure dropped to 10 mm. of water (Fig. 6*A*). At this time the fluid pressure began to rise more rapidly than usual; the respirations became deeper, and the arterial pressure rose in 10 minutes from 110 systolic and 75 diastolic to 160 systolic and 90 diastolic (Fig. 6*B*). Rhythmic swings in the arterial, jugular, and lumbar fluid pressures appeared, with about a minute between the peaks. Twenty milliliters of saline was added to the lumbar fluid space, bringing the pressure to 1,300 mm. of water, and then 12 ml. was withdrawn, returning the pressure to its initial level (Fig. 6*C*). The pressure spontaneously ran to 800 mm. Fluid was added to bring the pressure to 1,100 mm., and the pressure fell spontaneously to 800 mm. This displacement of the pressure was repeated several times over the next two hours, showing that the pressure was at equilibrium at 800 mm. (Fig 6*D*). The pressure recordings were discontinued, and the patient was returned to the ward.

There was little change in his clinical status for 12 hours, when the respirations became shallow, the pulse rapid and weak, and the blood pressure unobtainable. The patient died. Permission for autopsy was refused.

CASE 2.—J. S., a Negro woman aged 46, was admitted to the neurology service one day after the sudden onset of a severe frontal headache, followed by vomiting and stiffness of the neck. There was no loss of consciousness or localizing neurological signs. The grossly bloody spinal fluid had an initial pressure of 360 mm. of water. The headache and stiffness of the neck gradually improved over the next five days. On admission the blood pressure remained at the level it had been for several years previously, that of 150 systolic and 100 diastolic.

Five days after her admission a routine lumbar barography was performed except that the arterial pressure was not recorded because of unsuccessful needling. The bloody, xanthochromic spinal fluid had an initial pressure of 270 mm. of water. The patient became restless after the withdrawal of 50 ml. of spinal fluid, which lowered the pressure of 20 mm. of water; therefore no more fluid was withdrawn. This restlessness disappeared on addition of saline. After the addition of 42 ml. there developed numbness of the legs and a drawing pain in the right hip; the procedure was therefore terminated, with the fluid pressure at its initial level. The patient was returned to the ward, offering no complaints. After voiding 45 minutes later, she began to eat her lunch and then stated she was not hungry. Twenty minutes later she was found unresponsive, with stertorous breathing. Cheyne-Stokes breathing began; the pulse became rapid and weak, and she died 25 minutes after the onset of coma. Permission for autopsy was refused.

CASE 3.—N. P., a university student aged 24, was admitted on Feb. 9, 1953, in respiratory distress, deep coma, and decerebrate rigidity following an accident in which his car hit a brick wall. At operation he was found to have bloody ventricular fluid but no subdural hematoma.

He remained unconscious and decerebrate until June 15, at which time he was transferred to a hospital for chronic diseases.

Thirty-eight days after the injury a catheter was inserted in the right ventricle. After four unsuccessful attempts, further attempts to catheterize the left ventricle were not made. A needle was introduced into the lumbar subarachnoid fluid space and the pressures in the right internal jugular vein and the right internal carotid artery were recorded (Fig. 4). Fluid was added alternately to the lumbar space and to the right ventricle. After the induction of a "Cushing reaction," fluid was withdrawn from the ventricle, lowering the pressure to —350 mm. of water (Fig. 7). After repeated withdrawals, the pressure was allowed to return toward normal spontaneously. Two minutes later, with the pressure at — 80 mm. of water, the patient had a grand mal seizure and remained in status epilepticus, with frequent focal discharges beginning in the right side of the face. He was given deep sedation with 1 gm. of amobarbital (Amytal) sodium, but the twitchings continued for four hours. A half-hour after the induction of the seizure the pressure recordings were discontinued and a ventriculogram was made, which showed ventricles of normal size, with no midline shift. He was placed on treatment with diphenyl hydantoin for two days and has had no convulsions since.

SOME RELATIONSHIPS OF INTELLIGENCE, MENTAL EFFICIENCY, MENTAL DETERIORATION, AND DISEASE

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CLINICIANS frequently make observations and comments regarding the intellectual capacities of patients or of various disease groups, perhaps comparing one group with another or speculating upon the relationships between disease and intelligence. For example, it often has been expressed that the tubercle bacillus seems to increase the intellectual functions of those infected with tuberculosis. Patients, too, perhaps because of the "uniqueness" of their medical pictures, tend to consider themselves unique in other ways, as in their thought processes. Many patients may feel that their intellectual abilities have been greatly heightened or reduced. It has been noted that alcoholics believe that, since they differ from nonalcoholics in their reactions to alcohol, they must also differ in their thinking; and then they conclude that their thinking has been accelerated and that they are intellectually gifted. In the other direction are many patients with anxiety states, who believe that because they cannot resolve their emotional problems they must be rapidly deteriorating intellectually.

Within the area dealing with the relationships of intelligence to disease, the following questions often are raised but inconclusively answered:

1. Are there differences in intelligence among various disease groups? If so, how statistically significant are such differences?

2. Are certain disease groups more effective in the use of their intellectual abilities?

3. Do certain diseases, more than others, tend to induce mental deterioration? If so, what is the extent of such deterioration?

4. Are intellectual factors precursive of certain diseases? Do disease processes affect intelligence? What relationships exist between intelligence and pathology?

This paper presents data and interpretations which suggest tentative answers to these questions.

METHOD

Findings presented were obtained from approximately 1,000 patients who had received vocational counseling services at the Veterans Administration Hospital, Long Beach, during the period from 1946 to 1951. Patients were selected on the basis of their medical diagnoses and divided into nine disease groups: (1) postpoliomyelitis, (2) paraplegia, (3) tuberculosis, (4) psychoneurosis, (5) ulcer, (6) orthopedic (nonamputation disorders,) (7) amputation, (8) arthritis, and (9) alcoholism.

Each group contained 20 or more patients. The tuberculosis and paraplegia groups each contained more than 250 patients. In addition, a tenth group, of 25 nonhospitalized and nondisabled veterans who had received vocational counseling services within the hospital, was used as a control.

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Of the 1,000 patients, 668 had taken intelligence tests. Statistical analyses of the test results were made, and the groups were compared by their mean I.Q.'s. Statistical tests of significance were applied to the data, and interpretations of the findings were made.

Since it is known that language or verbal tests show relatively more stability than do nonlanguage or performance tests when conditions of time, trauma, or disease are imposed upon tested subjects, it has been assumed that the language functions remain relatively stable when deteriorating influences are applied, whereas the nonlanguage functions are relatively less stable when undergoing deteriorating changes. Because of these differences in test stability, it becomes possible to measure both mental efficiency and mental deterioration by means of the differential-test method.[1] This is accomplished by determining the ratio of the relatively stable language I.Q. to that of the relatively unstable nonlanguage I.Q. For example, if the language I.Q. is the same as the nonlanguage I.Q. in a tested subject, the ratio will be 1.0, and it will be assumed that mental efficiency is at 100% of capacity with no mental deterioration present. If the language I.Q. is more than the nonlanguage I.Q., the ratio will be less than 1.0, and it will be assumed that mental efficiency is less than 100% capacity and some mental deterioration has occurred. According to Wechsler,[1] should the nonlanguage I.Q. be higher than the language I.Q., this ratio might be an indication of psychopathy; Wechsler believes that 10% deviation or less above or below 100% may not be indicative of abnormal deviations.

Using Equation 1 for the determination of the percentage of mental efficiency and Equation 2 for the determination of the percentage of mental deterioration, percentages of mental efficiency and mental deficiency were determined for each of the clinical groups.

$$\frac{\text{Mean nonlanguage I. Q.}}{\text{Mean language I. Q.}} \times 100 = \begin{matrix}\text{Percentage}\\ \text{of mental}\\ \text{efficiency}\end{matrix} \qquad (1)$$

$$1 - \frac{\text{Mean nonlanguage I. Q.}}{\text{Mean language I. Q.}} \times 100 = \begin{matrix}\text{Percentage}\\ \text{of mental}\\ \text{deterioration}\end{matrix} \qquad (2)$$

In addition, data dealing with age and years of schooling completed were available, so that relationships of age and education to disease groups, mental efficiency, and mental deterioration were determined and interpreted.

A large number of the patients in this study initiated their requests for vocational counseling services; many others, who seemed to need assistance in the rehabilitation planning, were referred directly by ward physicians. Since selective factors, such as the physical and mental requirements for admission to the military services, requests for hospitalization, and the desire or need for vocational counseling were operating in the organization of the hospitalized disease groups studied, these groups are not typical of general population groups.

RESULTS

Age.—The range of ages for the total hospital group of 876 patients was 17 to 69 years. The mean age of this group was 29.8 years. For the disease groups, the range of mean ages was 26.3 years, for the postpoliomyelitis group, to 40.9 years for the alcoholism group. The groups with infectious and traumatic disease, such as postpoliomyelitis, paraplegia, and tuberculosis, were considerably younger than the progressive disease groups of arthritis and alcoholism.

Education.—For the total hospital group, the range of years of schooling completed was from 0 to 18 years. The mean years of schooling completed for the total hospital group was 10.9 years. The range for the means for the disease groups was from 9.8 years, for the amputation group, to 12.2 years, for the postpoliomyelitis group.

1. Wechsler, D.: Measurement of Adult Intelligence, Ed. 3, Baltimore, Williams & Wilkins Company, 1946.

A cursory inspection of the rank orders of the clinical groups in Table 1, in which age is compared with education, reveals that the younger groups appear to have had more schooling than had the older groups. The rank-order coefficient of correlation of age and education was found to be —0.82. Such a high negative correlation indicates a marked degree of relationship between age and education, with the younger groups consistently tending to have more education than the older groups. It may be that the younger groups were subject to more stringent school laws dealing with attendance, and thus were forced to spend more time in school,

TABLE 1.—*Age and Education of Disease Groups*

		Age				Education			
No.	Groups	No.	Rank Order	Mean Years	S. D.* Years	No.	Rank Order	Mean Years	S. D. Years
1	Postpoliomyelitis	35	1	26.3	4.6	33	9	12.2	1.5
2	Paraplegia	262	2	28.7	7.0	260	5	10.6	2.6
3	Tuberculosis	332	3	28.8	7.1	297	7	11.3	2.2
4	Psychoneurosis	74	4	30.9	7.4	72	8	11.5	2.2
5	Control	27	..	31.6	7.9	27	..	11.4	2.3
6	Ulcer	33	5	32.9	8.0	35	6	11.0	1.9
7	Orthopedic (nonamputation)	47	6	34.8	11.4	46	4	10.4	2.8
8	Amputation	21	7	39.1	12.0	20	1	9.8	2.4
9	Arthritis	40	8	40.2	10.1	35	2	10.1	2.7
10	Alcoholism	32	9	40.9	9.1	36	3	10.2	2.6
11	Total†	876	..	29.8	8.6	834	..	10.9	2.2

* Standard deviation.
† "Control" group statistics are not included in "Total" statistics.

TABLE 2.—*Mean I.Q.'s of Disease Groups*

No.	Groups	No. CMM	No. W-B	No. Otis	No. Total	Rank Order Total	Mean I. Q. Total	S. D. I. Q. Total
1	Amputation	10	0	3	13	1	102.9	21.0
2	Orthopedic	28	4	7	39	2	104.8	18.0
3	Ulcer	27	1	4	32	3	105.4	13.4
4	Paraplegia	153	30	38	221	4	107.5	16.0
5	Arthritis	30	4	2	36	5	107.8	18.9
6	Alcoholism	17	3	3	23	6	108.6	19.0
7	Tuberculosis	171	25	18	214	7	110.9	14.0
8	Psychoneurosis	48	13	8	69	8	112.6	15.5
9	Control	21	2	2	25	..	113.3	19.4
10	Postpoliomyelitis	18	3	0	21	9	115.4	11.9
11	Total*	502	83	83	668	..	109.0	17.5

* "Control" group statistics are not included in "total" statistics.

than were the older groups. Since positive correlations often have been found in studies correlating education with intelligence, it may be that the younger groups are more intelligent than the older groups. This point will be taken up shortly.

Intelligence.—The intelligence tests administered included the New California Short-Form Test of Mental Maturity—Advanced '47 S-Form; the Wechsler-Bellevue Intelligence Scale—Form I, and the Otis Self-Administering Tests of Mental Ability—Higher Examination. Both the California and the Wechsler test are so constructed as to provide separate measures of language and nonlanguage I. Q.'s. As previously mentioned, this makes possible the estimation of mental efficiency and mental deterioration percentages.

Table 2 presents the results of intelligence tests for 668 patients classified by disease groups. In effect, this Table is a hierarchy of the disease groups on the basis of their mean I. Q.'s. Studies made during World War I established a hierarchy of occupational groups based on intelligence test scores in which the professional and technical workers made the higher scores, while the unskilled and semiskilled workers made the lower scores.[2] A similar hierarchy was found to exist when the intelligence test scores of children were arranged according to their parents' occupations.[3]

In Table 2, it can be seen, the amputation and orthopedic groups have the lowest mean I. Q.'s yet these mean I. Q.'s are somewhat higher than might be expected from random samples of the adult population. The highest mean I. Q.'s were found in the postpoliomyelitis and psychoneurosis groups. These groups made considerably higher mean I. Q.'s than would be expected for the general adult population. The mean I. Q. for the total hospital group was 109.0, indicating high average intelligence.

The nine disease groups were combined to form four larger and fairly homogeneous disease categories. The ulcer and arthritis groups, since they were characterized by stress which led to a variety of emotional, endocrine, and metabolic

TABLE 3.—*Mean I.Q.'s of Disease Categories*

No.	Category	No.	Mean I. Q.
1	Stress	68	106.7
2	Traumatic	273	107.1
3	Infectious	235	111.3
4	Functional	92	111.6
5	Control	25	113.3
6	Total*	668	109.0

* "Control" group statistics are not included in "total" statistics.

changes, were combined and called the "stress" category; the paraplegia, orthopedic, and amputee groups were called the "traumatic" category; the tuberculosis and postpoliomyelitis groups formed the "infectious" category; and the psychoneurosis and alcoholism groups were combined into the "functional" category. When this was done, the categories from lowest to highest were stress, traumatic, infectious, and functional (Table 3).

What is the relationship between age and intelligence for the disease groups? By inspection, the younger groups seem to have the higher mean I. Q.'s; the rank-order coefficient of correlation between age and mean I. Q. was found to be —0.45, pointing to a relationship in which the younger disease groups tend to have the higher mean I. Q.'s, while the older disease groups tend to have the lower mean I. Q.'s

Other studies have shown consistent relationships between educational achievements and intelligence; persons having the higher intelligence test scores also tend to complete more years of schooling, as well as to complete the more difficult academic, professional, and technical training courses. In this study, the rank-

2. Psychological Examining in the United States Army, Memoirs, National Academy of Sciences, Washington, D. C., Vol. 15., 1921.

3. Hildreth, G.: Occupational Status and Intelligence, Personnel J. **13**:153-157, 1943.

order coefficient of correlation between years of schooling completed and mean I. Q. for the disease groups was 0.73. This high positive correlation suggests a marked relationship, in which the more intelligent disease groups tend to have completed the most years of schooling.

Data have been presented which indicate that there are differences among disease groups on intelligence test performances. How significant are these differences? Could the differences found be due to chance, or are they real differences which could be expected to occur consistently? The statistical significance of the differences between each combination of the groups studied was determined by computing the critical ratios between each combination of groups. Critical ratios of 2.0 or higher indicate that the probability for the mean I. Q. differences occurring would be 5 chances in 100, or would be statistically significant at the 5% level of confidence. Differences with critical ratios of 3.0 or higher occur with a probability of 1 chance in 100 and are statistically significant at the 1% level of confidence.

TABLE 4.—*Matrix of Critical Ratios for Group Differences in Mean Intelligence Quotients*

	P-P	Para	TB	PN	Cont	Ulc	Orth	Amp	Arth	Alc	Total
Postpoliomyelitis	..	..	..	..	..	..	..	..	..	..	..
Paraplegia	2.8	..	..	..	..	..	..	..	..	..	..
Tuberculosis	1.6	2.3	..	..	..	..	..	..	..	..	..
Psychoneurosis	1.3	2.3	0.8	..	..	..	..	..	..	..	..
Control	0.7	3.2	1.4	0.3	..	..	..	..	..	..	..
Ulcer	2.7	0.8	2.1	2.3	2.8	..	..	..	..	..	..
Orthopedic	2.7	0.9	2.0	2.2	2.7	0.02	..	..	..	..	..
Amputation	1.8	0.8	1.4	1.6	1.7	0.4	0.3	..	..	..	..
Arthritis	1.9	0.1	0.9	1.3	1.6	0.6	0.7	0.7	..	..	..
Alcoholism	1.4	0.3	0.6	0.9	1.1	0.7	0.8	0.8	0.2	..	..
Total	2.4	1.0	1.6	2.3	2.7	1.4	1.4	1.1	0.4	0.1	..

Examination of Table 4, a matrix of the critical ratios, reveals 15 critical ratios of 2.0 or more. One of these critical ratios is 3.2.

Differences significant at least at the 5% level of confidence were found between the following group comparisons:

Groups Compared	Critical Ratios
Postpoliomyelitis vs. total	2.4
Paraplegia vs. postpoliomyelitis	2.8
Paraplegia vs. tuberculosis	2.3
Paraplegia vs. psychoneurosis	2.3
Paraplegia vs. control	3.2
Psychoneurosis vs. total	2.3
Control vs. total	2.7
Ulcer vs. postpoliomyelitis	2.7
Ulcer vs. tuberculosis	2.1
Ulcer vs. psychoneurosis	2.3
Ulcer vs. control	2.8
Orthopedic vs. postpoliomyelitis	2.7
Orthopedic vs. tuberculosis	2.0
Orthopedic vs. psychoneurosis	2.2
Orthopedic vs. control	2.7

Since a large group of patients took the California Mental Maturity test, a separate analysis of this test was made. On this test, a mean I. Q. of 109.9 was found for a group of 502 patients. The mean language I. Q. was 112.3, and the mean nonlanguage I. Q. was 106.6. The postpoliomyelitis group made the highest mean I. Q.'s on language, nonlanguage and total test performances. The lowest

mean I. Q. for the total test—103.1—was made by the orthopedic group. The lowest mean language I. Q.—104.5—was made by the amputation group, and the lowest mean nonlanguage I. Q.—96.2—was made by the arthritis group. Both the postpoliomyelitis and the psychoneurosis group made higher mean language I. Q.'s and total score I. Q.'s than did the tuberculosis group; only the postpoliomyelitis group made a higher mean nonlanguage I. Q. than did the tuberculosis group (Table 5).

On the California Mental Maturity test, the rank-order coefficient of correlation for mean language I. Q. versus mean nonlanguage I. Q. was 0.34; for mean language I. Q. versus mean total I. Q., it was 0.77, and for mean nonlanguage I. Q. versus mean total I. Q. it was 0.77.

TABLE 5.—*Mean Intelligence Quotients of California Mental Maturity Test of Disease Groups*

No.	Group	No. L*	Rank Order L	Mean L I. Q.	S. D. L	No. N-L*	Rank Order N-L	Mean N-L I. Q.	S. D. N-L	No. T*	Rank Order T	Mean T I. Q.	S. D. T
1	Amputation	10	1	104.5	17.0	10	7	109.5	18.6	10	4	106.5	8.7
2	Orthopedic	25	2	105.7	16.6	28	3	101.3	23.4	28	1	103.1	19.7
3	Paraplegia	153	3	103.7	21.1	158	6	107.5	21.2	153	6	108.2	18.6
4	Ulcer	27	4	110.4	18.1	27	2	99.0	19.5	27	2	105.2	15.7
5	Arthritis	30	5	111.8	21.5	30	1	96.2	20.7	30	3	106.8	19.8
6	Alcoholism	18	6	112.8	19.7	18	4	101.7	25.3	17	5	107.4	19.8
7	Control	22	..	113.1	18.6	22	..	109.5	26.6	21	..	113.5	22.3
8	Tuberculosis	172	7	114.0	19.5	171	8	111.8	20.1	171	7	112.4	17.6
9	Psychoneurosis	44	8	116.8	19.1	44	5	103.6	20.1	48	8	113.0	17.4
10	Postpoliomyelitis	18	9	120.6	16.0	18	9	112.5	20.5	18	9	115.6	13.0
11	Total†	497	..	112.3	20.2	504	..	106.6	21.9	502	..	109.9	18.1

* L indicates language score; N-L, nonlanguage score, and T, total-test performance.
† "Control" group statistics are not included in "total" statistics.

An analysis of the mean scores made on the Wechsler-Bellevue test and the Otis test follows:

Test	No.	Mean I. Q.	S. D. I. Q.
Wechsler verbal	87	113.5	19.3
Wechsler performance	83	108.5	17.4
Wechsler total	83	110.5	16.7
Otis total	83	103.7	13.3

Mental Efficiency and Mental Deterioration.—Using Equations 1 and 2, percentages representing mental efficiency and mental deterioration were determined for each of the disease groups. The three most efficient groups were found to be the amputation, tuberculosis, and paraplegia groups. The three least efficient groups were the ulcer, psychoneurosis, and arthritis groups. The amputation group showed a mental efficiency of 104.8%. Since this is only 4.8% in excess of 100%, this percentage should not be interpreted as indicating group psychopathy. It might indicate a slight tendency on the part of the amputation group toward nonconforming behavior, or perhaps might point toward carelessness or recklessness.

All the other groups showed ratios of less than 100%. Only three groups showed 10% of mental deterioration or more. These were the ulcer, psychoneurosis, and arthritis groups. The arthritis group had the largest ratio of mental deterioration—14.0%.

Similar determinations were made for disease groups having had 10 or more patients who took the Wechsler test. These included the tuberculosis, paraplegia,

and psychoneurosis groups. Eighty-seven patients comprised the "total" group which took the Wechsler test. In three of the four comparisons of the Wechsler test with the California Mental Maturity test there were but slight differences in the percentages of mental deterioration, but in a sample of 13 psychoneurosis patients taking the Wechsler test when compared with a sample of 44 psychoneurosis patients taking the California Mental Maturity test, there was a marked difference in mental deterioration estimates. On the Wechsler test the mental deterioration was 3.3%, while on the California Mental Maturity test the deterioration was 11.3% (Table 6).

The rank-order coefficient of correlation between the total mean I. Q. and the percentage of mental deterioration was —0.65, indicating a fairly strong trend for the groups with more mental deterioration toward the lower mean I. Q.'s and for the groups with the least amount of mental deterioration toward the highest mean I. Q.'s.

TABLE 6.—*Percentages of Mental Efficiency and Mental Deterioration of Disease Groups*

No.	Group	Mean CMM L. I. Q.	Mean CMM N.L. I. Q.	$\frac{\text{N.L. I. Q.}}{\text{L. I. Q.}} \times 100$ % Ment. Effic.	$1 - \frac{\text{N.L. I. Q.}}{\text{L. I. Q.}} \times 100$ % Ment. Deter.	Rank Order Ment. Effic.	No. W-B	W-B % Ment. Effic.	W-B % Ment. Deter.
1	Arthritis	111.8	96.2	86.0	—14.0	1	..	.....	.....
2	Psychoneurosis	116.8	103.6	88.7	—11.3	2	13	96.7	—3.3
3	Ulcer	110.4	99.0	89.7	—10.3	3	..	.....	.....
4	Alcoholism	112.8	101.7	90.2	— 9.8	4	..	.....	.....
5	Postpoliomyelitis	120.6	112.5	93.3	— 6.7	5	..	.....	.....
6	Orthopedic	105.7	101.3	95.8	— 4.2	6	..	.....	.....
7	Control	113.1	109.5	96.8	— 3.2	..	..	.....	.....
8	Paraplegia	109.7	107.5	97.9	— 2.1	7	30	94.7	—5.3
9	Tuberculosis	114.0	111.8	98.1	— 1.9	8	26	97.7	—2.3
10	Amputation	104.5	109.5	104.8	+ 4.8	9	..	.....	.....
11	Total*	112.3	106.6	94.9	— 5.1	..	82†	96.6	—4.4

* "Control" group statistics are not included in "total" statistics.
† This figure includes other disease groups besides the three above.

In correlating the rank orders of the disease groups for age and mental deterioration, a correlation coefficient of 0.27 was found, pointing to a slight trend for the older groups toward more mental deterioration.

The rank-order coefficient of correlation between years of schooling completed and mental deterioration was 0.12. Such a low correlation would indicate very little, if any, relationship between education completed and mental deterioration.

COMMENT

In view of the group-selection factors present, it was expected that the total hospital group studied would be of higher than average intelligence. Such was the case, the mean I. Q. of the total group being 109.0.

It is interesting to note that the tuberculosis group, although of high average intelligence, was not the most intelligent disease group. Two other disease groups, as well as the control group, made higher mean I. Q.'s than did the tuberculosis group. However, these differences were not statistically significant. Barker,

Wright, and Gonick,[4] summarizing a number of paper-and-pencil-test and Rorschach studies dealing with the intelligence of tuberculosis patients, concluded that tuberculosis may be associated with slight increases in intellectual functioning and that no evidence of intellectual regression or mental deterioration was indicated. This opinion is in accord with the findings of this study.

Since the treatment of tuberculosis and psychoneurosis involves long periods of time, considerable insight and cooperation on the part of the patients would be necessary if treatment is to be successful. It is assumed that the more alert patients seek out, obtain, and maintain prolonged hospitalization and treatment. Such an assumption might explain the higher mean I. Q.'s for the tuberculosis and psychoneurosis groups.

It is believed that the range and distribution of intelligence test scores for the tuberculosis and psychoneurosis groups outside hospitals approximate those of the general population. No studies of the intelligence of nonhospitalized persons with tuberculosis or psychoneurosis were available to me. Since these diseases do not bring about frequent sudden attacks of severe pain and discomfort, the immediate need for the relief of pain is seldom experienced. Therefore, only those who recognize the serious and protracted nature of these diseases will seek and carry through treatment. It is believed that this results in the more intelligent persons with tuberculosis and psychoneurosis seeking treatment, becoming hospitalized, and thus comprising the hospital groups. Such samples, it appears, form negatively skewed curves.

Barker, Wright, and Gonick [4] pointed to evidence that adults physically handicapped by crippling tend to have slightly lower intelligence test scores than do the nonhandicapped. In the present study, it was found that the amputation, orthopedic, paraplegia, and arthritis groups were below the means both for the total hospital group and for the control group. On the other hand, the postpoliomyelitis group made considerably higher mean I. Q.'s than either the total hospital or the control group. The control group made significantly higher scores than the orthopedic and paraplegia groups. This is in line with the earlier studies, which indicate that there is a tendency for "crippled" groups to have slightly lower mean I. Q.'s than "noncrippled" groups. The present study found, however, that this trend did not apply to the postpoliomyelitis group.

How could the lower I. Q.'s for the amputation and orthopedic groups be interpreted? A large number of these patients had been hospitalized because of accidents. On investigation of their work backgrounds, the impression formed was that many of these patients had done hard physical work, requiring little skill or training, or had worked in situations somewhat more dangerous than might be expected. Frequently their jobs involved both hard work and danger. Among the amputation and orthopedic patients there had been railroad, oil field, and logging camp workers, truck drivers, and motorcyclists. Since the amputation and orthopedic groups had lower mean I. Q.'s and less education, it is reasonable to assume that they had less learning ability and less training for work and were handicapped in obtaining the more skilled and relatively safer jobs. As a result, they drifted into work which was available to them, rather than seeking specific jobs for which they

4. Barker, R. G.; Wright, B. A., and Gonick, M. R.: Adjustment to Physical Handicap and Illness: A Survey of the Social Psychology of Physique and Disability, Bulletin 55, Social Science Research Council of New York, 1946.

had been trained. Lack of training, together with exposure to dangerous situations, made these patients subject to more accidents. The more unskilled, semiskilled, and duller workers seemed to have the amputations and the orthopedic disabilities.

Persons requiring attention for amputation or orthopedic disabilities—which may be very painful—will seek immediate medical care. This results in most such persons placing themselves at once under medical supervision. Amputation and orthopedic groups in hospitals, it would seem, would be quite representative of such groups outside hospitals. It may be that there is a narrower range of intelligence for amputation and orthopedic groups than for tuberculosis and psychoneurosis groups. This narrower range would include a larger percentage of the middle and lower segments and a smaller percentage of the upper half of the normal distribution curve for the general population. Such a curve could be described as positively skewed.

It has been observed in many instances that prior to the onset of poliomyelitis, postpoliomyelitis patients had been working strenuously and excessively. From interviews with such patients, the impression was formed that many of the postpoliomyelitis patients had been unusually aggressive, ambitious, and deeply engrossed in their work. In addition, they appeared to be making good work progress. Indications of successful work activities point to the early recognition of interest and motivations and the early selection of stimulating and rewarding career endeavors. In addition, since the postpoliomyelitis group leads the disease groups in education, the conclusion might be reached that these patients had good work preparation. It may be that postpoliomyelitis patients, because of higher intelligence, developed more interests, skills, and motivations; they worked harder; this increased work load lowered their resistance to disease, and they became more susceptible to poliomyelitis infection. This may be an instance of persons whose high intelligence creates situations of increased fatigue and decreased resistance to disease, leading to infection. The distribution curve of the postpoliomyelitis group seems to be similar to that of the amputation and orthopedic groups, except that it is negatively skewed or weighted with a larger percentage of intelligence test scores from the upper half of the normal distribution curve and a smaller percentage from the lower half of the normal curve.

It might be expected that the more intelligent persons would have more information about hygiene, be more likely to use prophylactic measures, and thus be more likely to prevent infections than would the less intelligent. Yet the findings in this study point in the opposite direction. The less intelligent groups have the traumatic disorders, while the more intelligent groups have the infectious diseases.

It was stated that the high intelligence of the postpoliomyelitis group was only an indirect contributing factor to the onset of poliomyelitis. In the case of the tuberculosis group, however, high intelligence did not bring on infection, but, rather, led to the early recognition for treatment and the acceptance of hospitalization. For the amputation and orthopedic groups, lower intelligence could not be interpreted to have caused the accidents but probably did contribute to the creation of accident situations.

As far as the size of the mean I. Q. is concerned, there does not appear to be any clear relationship between emotional and intellectual factors. This comment is based on the standings of the disease categories: The stress category, composed

of the ulcer and arthritis groups, had the lowest mean I. Q., while the functional category, made up of the psychoneurosis and alcoholism groups, had the highest mean I. Q. A different conclusion was reached when an analysis of the percentages of mental deterioration was made.

Statistically significant differences between the various disease groups were present. Both the postpoliomyelitis and the psychoneurosis group were significantly higher in mean I. Q.'s than the total hospital group; the control group was significantly higher than the paraplegia, ulcer, orthopedic, and total hospital groups; the paraplegia group was significantly lower than the postpoliomyelitis, tuberculosis, and psychoneurosis groups; the ulcer group was significantly lower than the postpoliomyelitis, tuberculosis, and psychoneurosis groups, and the orthopedic group was significantly lower than the paraplegia, tuberculosis, and psychoneurosis groups. These findings point to the presence of real differences in mean I. Q.'s among the various disease groups.

From an examination of the ratios indicative of mental efficiency and mental deterioration, it appears that the findings for the total hospital group, although slightly below the percentage of mental efficiency and slightly above the percentage of mental deterioration of the control group, are well within the normal limits of the ratios for the nonhospital population. Only the arthritis, psychoneurosis, and ulcer groups showed ratios of mental deterioration above 10%. The alcoholic group had 9.8% of mental deterioration. The four groups with the largest percentages of mental deterioration also appeared to have the most emotional factors related to their disorders. The infectious and traumatic disease groups showed the lowest percentages of mental deterioration.

Mental deterioration could be caused by conditions of damage to the cerebral cortex or cortical dysfunction of functional etiology, or combinations of these two categories of factors. In the four groups with the largest percentages of mental deterioration, the general causative factor of mental deterioration appeared to be one due to functional disturbances of cortical associations. Quite likely in some of the alcoholic patients, as perhaps in other patients, organic damage may also have been present. It was somewhat unexpected to find the arthritis group with the largest percentage of mental deterioration. The postpoliomyelitis and alcoholism groups were expected to have the largest percentages of mental deterioration because of their apparent cortical damage. The alcoholism group ranked fourth, and the postpoliomyelitis group ranked fifth. The postpoliomyelitis group had only a slightly larger mean percentage of mental deterioration than had the total hospital group. The paraplegia, tuberculosis, and amputation groups showed the least amount of mental deterioration.

SUMMARY AND CONCLUSIONS

There were marked mean age differences among the various disease groups.

There also were differences among the disease groups in the amount of education completed.

A rank-order coefficient of correlation between age and education of —0.73 indicated that the younger disease groups tended to have more education than the older disease groups.

The mean I. Q.'s of nine disease groups and a total hospital group of 668 patients were determined. The mean I. Q. for the total group was 109.0.

A rank-order coefficient of correlation of —0.45 between intelligence and age indicated that the younger disease groups tended to have the higher mean I. Q.'s.

A rank-order coefficient of correlation of 0.73 between intelligence and years of schooling completed indicated that the disease groups with the higher mean I. Q.'s tended to have the most schooling.

Differences in mean intelligence were found among the various disease groups tested. Fifteen differences in mean I. Q. among the various disease groups were statistically significant at the 5% and higher levels of confidence.

The postpoliomyelitis, psychoneurosis, and tuberculosis groups had the highest mean I. Q.'s, while the amputation, orthopedic, and ulcer groups had the lowest mean I. Q.'s.

A separate analysis of approximately 500 test scores on the California Mental Maturity test was made of all the groups studied.

Percentages of mental efficiency and mental deterioration were determined for each of the disease groups. Three disease groups—arthritis, psychoneurosis, and ulcer—had more than 10% mental deterioration, suggesting the presence of significant organic damage or disorganization.

A rank-order coefficient of correlation between intelligence and mental deterioration was —0.65, which indicated that the groups with the lower mean I. Q.'s tended to have more mental deterioration.

A rank-order coefficient of correlation of 0.27 between mental deterioration and age was found, and a coefficient of 0.12 between mental deterioration and years of schooling was found.

It was concluded that persons with psychoneurosis and tuberculosis who also have high intelligence are more likely to seek and obtain prolonged treatment. There was no evidence that high intelligence leads to tuberculosis or psychoneurosis. There was some evidence that poliomyelitis patients of high intelligence tend to overwork and become excessively fatigued. Such a condition may be a factor leading to poliomyelitis infection.

Jobs requiring hard physical work and danger are often held by men with low I. Q.'s and little schooling. Such men are more prone to have accidents. Low I. Q.'s, together with the elements of hard labor and danger, may be factors in creating accidents which lead to amputation and orthopedic disabilities.

PITUITARY-ADRENAL CORTEX REACTIVITY IN SCHIZOPHRENIC PATIENTS

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CONSIDERABLE controversy has been raised over a period of several years concerning the reactivity of the pituitary-adrenal cortex system in schizophrenic patients. Many papers have been presented, and much conflicting evidence has been offered.

In 1934 Freeman and Hoskins [1] reported an elevated reactivity of schizophrenic patients with respect to the blood pressure-increasing effects of a glycerin extract of the adrenal cortex. Loehner,[2] in 1940, remarked on similarities between schizophrenia and hypoadrenal states. The same theme was taken up by Haynes and Carlisle in 1941 [3] and 1943 [4] and by Williams [5] in 1943. Meduna [6] implicated abnormality of the adrenals in a "dysfunction of the carbohydrate regulating mechanism" of schizophrenia, a theory which he proposed in 1943. A series of studies was presented by Pincus, Hoagland, Elmadjian, Freeman, and associates [7] between 1946

From the Veterans Administration Hospital, Palo Alto, Calif., with which the author affiliated during the course of the study.

1. Freeman, H., and Hoskins, R. G.: Comparative Sensitiveness of Schizophrenic and Normal Subjects to Glycerin Extract of Adrenal Cortex, Endocrinology **18**:576, 1934.

2. Loehner, C. A.: Further Observations on the Use of Adrenal Cortex Extract in the Psychotic and Non-Psychotic Patient, Endocrinology **27**:378, 1940.

3. Haynes, H. J., and Carlisle, C. L.: The Treatment of Schizophrenia with Desoxycorticosterone Acetate, M. Bull. Vet. Admin. **18**:141, 1941.

4. Haynes, H. J., and Carlisle, C. L.: The Treatment of Schizophrenia with Desoxycorticosterone Acetate (Supplementary Report), M. Bull. Vet. Admin. **19**:40, 1943.

5. Williams, E. H.: Some Clinical Observations of Nervous Disorders with Adrenal Involvement, Dis. Nerv. System **4**:185, 1943.

6. Meduna, L. J.: Dyshormonism in Psychoses and Its Correction by Shock, J. Nerv. & Ment. Dis. **98**:507,1943.

7. Pincus, G., and Elmadjian, F.: A Study of Diurnal Variations in Circulating Lymphocytes in Normal and Psychotic Subjects, J. Clin. Endocrinol. **6**:287, 1946; The Lymphocyte Response to Heat Stress in Normal and Psychotic Subjects, ibid. **6**:295, 1946. Hoagland, H.; Elmadjian, F., and Pincus, G.: Stressful Psychomotor Performance and Adrenal Cortical Function as Indicated by the Lymphocyte Response, ibid. **6**:301, 1946. Elmadjian, F., and Freeman, H.: The Relationship Between Blood Sugar and Lymphocyte Levels in Normal and Psychotic Subjects, Psychosom. Med. **9**:226, 1947. Phillips, L., and Elmadjian, F.: A Rorschach Tension Score and the Diurnal Lymphocyte Curve in Psychotic Subjects, ibid. **9**:364, 1947. Elmadjian, F.; Freeman, H.; Hoagland, H., and Pincus, G.: Adrenal Function in Mental Disease, Recent Progr. Hormone Res. **4**:291, 1949. Pincus, G.; Hoagland, H.; Freeman, H.; Elmadjian, F., and Romanoff, L. P.: A Study of Pituitary-Adrenocortical Function in Normal and Psychotic Men, Psychosom. Med. **11**:74, 1949. Pincus, G.; Schenker, V.; Elmadjian, F., and Hoagland, H.: Responsivity of Schizophrenic Men to Pituitary Adrenocorticotrophin, ibid. **11**:146, 1949. Hoagland, H., and Pincus, G.: The Nature of the Adrenal Stress Response Failure in Schizo-

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and 1952. These studies purported to demonstrate "a species of hypoadrenalism" present in schizophrenic patients. Agreement with this view was reported in information offered in 1950 by Friedlander, Perrault, Turner, and Gottfried [8] and by Cleghorn and Graham.[9] Faurbye, Vestergaard, Kobbernagel, and Nielsen [10] described a "slight relative adrenal cortex insufficiency" in their cases of chronic schizophrenia. In 1952, Ashby [11] suggested that an abnormal adrenocortical steriod production was operative in a reported case of periodic catatonia, and Rowntree and Kay [12] presented evidence for an abnormal dissociation of adrenal cortex steroids in two cases of recurrent schizophrenia.

However, in 1949 Parsons, Gildea, Ronzoni, and Hulbert [13] concluded, on the basis of experimental studies, that no impairment of the pituitary-adrenal cortex system was specific to schizophrenia. Stein, Ronzoni, and Gildea [14] repeated this view in a paper published in 1951. Altschule and his associates—Promisel, Parkhurst, and Grunebaum,[15] in 1950; Grunebaum,[16] in 1950; Siegel and Mora-Castaneda,[17] in 1951, and Siegel, Restaino, and Parkhurst,[18] in 1952—felt that there was no adrenal cortex impairment in the schizophrenic patients whom they had tested. No evidence of decreased adrenal cortex reactivity was found by Perloff,

phrenic Man, J. Nerv. & Ment. Dis. **111**:434, 1950. Pincus, G., and Hoagland, H.: Adrenal Cortical Responses to Stress in Normal Men and in Those with Personality Disorder: Some Stress Responses in Normal and Psychotic Subjects, Am. J. Psychiat. **106**:641, 1950. Freeman, H., and Elmadjian, F.: Carbohydrate and Lymphoid Studies in Schizophrenia, ibid. **106**:660, 1950. Hoagland, H., and Pincus, G.: Pituitary-Adrenocortical Function in Patients with Severe Personality Disorders, Proceedings of the First Clinical ACTH Conference, edited by J. R. Mote, Philadelphia, The Blakiston Company, 1950, p. 544. Mittelman, A.; Romanoff, L. P.; Pincus, G., and Hoagland, H.: Neutral Steroid Excretion by Normal and Schizophrenic Men, J. Clin. Endocrinol. **12**:831, 1952.

8. Friedlander, J. H.; Perrault, R.; Turner, W. J., and Gottfried, S. P.: Adrenocortical Response to Physiologic Stress in Schizophrenia, Psychosom. Med. **12**:86, 1950.

9. Cleghorn, R. A., and Graham, B. F.: Studies of Adrenal Cortical Activity in Psychoneurotic Subjects, Am. J. Psychiat. **106**:668, 1950.

10. Faurbye, A.; Vestergaard, P.; Kobbernagel, F., and Nielsen, A.: Adrenal Cortical Function in Chronic Schizophrenia (Stress, Adrenaline-Test, ACTH-Test), Acta endocrinol. **8**:215, 1951.

11. Ashby, W. R.: Adrenal Cortical Function and Response to Convulsive Therapy in a Case of Periodic Catatonia, J. Ment. Sc. (No. 410) **98**:81, 1952.

12. Rowntree, D. W., and Kay, W. W.: Clinical, Biochemical, and Physiological Studies in Cases of Recurrent Schizophrenia, J. Ment. Sc. (No. 410) **98**:100, 1952.

13. Parsons, E. H.; Gildea, E. F.; Ronzoni, E., and Hulbert, S. Z.: Comparative Lymphocytic and Biochemical Responses of Patients with Schizophrenia and Affective Disorders to Electroshock, Insulin Shock, and Epinephrine, Am. J. Psychiat. **105**:573, 1949.

14. Stein, M.; Ronzoni, E., and Gildea, E. F.: Physiological Responses to Heat Stress and ACTH of Normal and Schizophrenic Subjects, Am. J. Psychiat. **108**:450, 1951.

15. Altschule, M. D.; Promisel, E.; Parkhurst, B. H., and Grunebaum, H.: Effects of ACTH in Patients with Mental Disease, Arch. Neurol. & Psychiat. **64**:641, 1950.

16. Altschule, M. D., and Grunebaum, H.: Concentration of Sodium in Thermal Sweat in Patients with Mental Disease, J. Clin. Invest. **29**:796, 1950.

17. Altschule, M. D.; Siegel, E., and Mora-Castaneda, F.: Significance of Rise in Blood Sugar Level After Injection of Epinephrine in Mental Disease, A. M. A. Arch. Neurol. & Psychiat. **65**:589, 1951.

18. Altschule, M. D.; Siegel, E. P.; Restaino, R. M., and Parkhurst, G. H.: Blood Eosinophilic Leucocytes in Mental Disease, A. M. A. Arch. Neurol. & Psychiat. **67**:228, 1952.

Levy, and Despopoulos (1952)[19] in a group of schizophrenic patients studied before brain surgery. In 1952, Hiatt, Rothwell, and Horwitt [20] represented their studies as demonstration that there was no specific adrenal cortex deficiency in schizophrenia.

This conflict has appeared also in the series of reports concerning the therapeutic effectiveness of various adrenal cortex manipulations as treatment of schizophrenia. Articles by Moore,[21] in 1942; Allen and Broster,[22] in 1945; Loehner,[23] in 1938; Cohn, Karnosh, and Stecher,[24] in 1951, and Sackler, Sackler, Sackler, Tui, and Siegel, in 1951 [25] all claim beneficial use of such manipulations. On the other hand, Dax, Smith, and Reitman,[26] in 1947; Glaser and Hoch,[27] in 1951, and Rees and King,[28] in 1951 and 1952, found little response to adrenal cortex-oriented therapy in their schizophrenic patients.

In physiologic studies of various somatotherapy techniques, the question of the adrenal cortex reactivity of schizophrenic patients has frequently been raised. Hemphill, MacLeod, and Reiss [29] pointed out in 1942 that excretion of some of the adrenal cortex end-products—17-ketosteroids—was increased in schizophrenic patients during electroshock therapy and after prefrontal leucotomy. Tietz and Birnbaum,[30] in 1942, concluded that insulin shock therapy promoted sympathicoadrenal stability as one of its beneficial effects. In 1948 Mikkelsen and Hutchens [31] presented their evidence that electroshock therapy stimulated adrenal cortex function as part of its effectiveness in treatment of schizophrenia. Simon, Bowman, and

19. Perloff, W. H.; Levy, L. M., and Despopoulos, A.: The Eosinophil Response to Stress in Patients with Surgically Produced Thalamic and Hypothalamic Lesions, J. Clin. Endocrinol. **12**:36, 1952.

20. Hiatt, H. H.; Rothwell, W. S., and Horwitt, M. K.: Eosinopenia Produced by ACTH in Patients with Schizophrenia, Proc. Soc. Exper. Biol. & Med. **79**:707, 1952.

21. Moore, T. V.: Physiological Factors in Treatment of Mental Disorders, Psychiat. Quart. **16**:565, 1942.

22. Allen, C., and Broster, L. R.: A Further Case of Paranoid Psychosis Successfully Treated by Adrenalectomy, Brit. M. J. **1**:696, 1945.

23. Loehner, C. A.: The Therapeutic Effect of Adrenal Cortex Extract on the Psychotic Patient, Endocrinology **23**:507, 1938.

24. Cohn, J. B.; Karnosh, L. J., and Stecher, R. M.: Clinical Trials with Cortisone in Treatment of Chronic Schizophrenia, Dis. Nerv. System **12**:291, 1951.

25. van Ophuijsen, J. H. W.; Sackler, R. R.; Sackler, M. D.; Tui, C.; Siegel, M. G., and Sackler, A. M.: Endocrinologic Orientation to Psychiatric Disorders, J. Clin. & Exper. Psychopath. **12**:1, 1951.

26. Dax, E. C.; Radley Smith, E. J., and Reitman, F.: Adrenalectomy in Mental Disease, Brit. M. J. **1**:215, 1947.

27. Glaser, G. H., and Hoch, P. H.: Observations on the Effect of Corticotropin in Schizophrenia: Preliminary Report, A. M. A. Arch. Neurol. & Psychiat. **66**:697, 1951.

28. Rees, L., and King, G. M.: Desoxycortone Acetate and Ascorbic Acid in Treatment of Schizophrenia, J. Ment. Sc. **97**:376, 1951; Cortisone in the Treatment of Schizophrenia, ibid. (No. 412) **98**:401, 1952.

29. Hemphill, R. E.; MacLeod, L. D., and Reiss, M.: Changes in Output of 17-Ketosteroids After Electric Shock Treatment, Pre-Frontal Leucotomy, and Other Procedures, J. Ment. Sc. **88**:554, 1942.

30. Tietz, E. B., and Birnbaum, S. M.: Level of Adrenocortical Substance in Blood During Hypoglycemic Treatments for Schizophrenia, Am. J. Psychiat. **99**:75, 1942.

31. Mikkelsen, W. P., and Hutchens, T. T.: Lymphopenia Following Electrically Induced Convulsions in Male Psychotic Patients, Endocrinology **42**:394, 1948.

Halliday,[32] in 1948, described sympathicoadrenal-stimulating effects of electronarcosis and electroshock therapy (grand and petit mal types) but did not feel this element to be central to the issues of either the illness or the therapy. Rees,[33] in 1949, reported adrenal cortex-stimulating effects of electronarcosis. Other investigators subsequently presented evidence demonstrating the adrenocortical activation effects of electroconvulsive therapy—Ashby,[34] in 1949; Altschule, Altschule, and Tillotson,[35] in 1949; Altschule, Parkhurst, and Tillotson,[36] in 1949; Altschule and Tillotson,[37] in 1949; Altschule and Parkhurst,[38] in 1950; Grunebaum and Altschule,[39] in 1950; Graham and Cleghorn,[40] in 1951; Michael and Brown,[41] in 1951, and Ashby,[11] in 1952. Insulin shock and electronarcosis were also further discussed with regard to their adrenal cortex-activating function by Taylor, Gross and Ruby,[42] in 1951; Gottfried and Minsky,[43] in 1951, and Shattock and Micklem,[44] in 1952.

Many of these investigators implied belief that the benefit offered by somatotherapy to the schizophrenic patient was associated with its ability to increase the activity of the patient's pituitary-adrenal cortex system. Other authors have agreed that somatotherapy increases that system activity but have denied that there is any specific correlation between that ability to increase function and the ability to produce clinical improvement in schizophrenia—they include Stern, Askonas, and Cullen,[45]

32. Simon, A.; Bowman, K. M., and Halliday, N.: Studies in Electronarcosis Therapy, Physiological Effects in Electronarcosis and Electroshock, J. Nerv. & Ment. Dis. **107**:358, 1948.

33. Rees, L.: Physiological Concomitants of Electronarcosis, J. Ment. Sc. **95**:162, 1949.

34. Ashby, W. R.: The Effects of Convulsive Therapy on the Excretion of Cortins and Ketosteroids, J. Ment. Sc. **95**:275, 1949.

35. Altschule, M. D.; Altschule, L. H., and Tillotson, K. J.: Changes in Leukocytes of the Blood in Man After Electrically Induced Convulsions, Arch. Neurol. & Psychiat. **62**:624, 1949; Changes in Urinary Uric Acid-Creatinine Ratio After Electrically Induced Convulsions in Man, J. Clin. Endocrinol. **9**:548, 1949.

36. Altschule, M. D.; Parkhurst, B. H., and Tillotson, K. J.: Decreases in Blood Eosinophilic Leukocytes After Electrically Induced Convulsions in Man, J. Clin. Endocrinol. **9**:440, 1949.

37. Altschule, M. D., and Tillotson, K. J.: The Effect of Electroconclusive Therapy on Water Metabolism in Psychotic Patients, Am. J. Psychiat. **105**:829, 1949; A Report on Further Physiological Observations Associated with Electroshock Therapy, J. Nerv. & Ment. Dis. **110**:540, 1949.

38. Altschule, M. D., and Parkhurst, B. H.: Effect of Treatment on the Excretion of 17-Ketosteroids in Patients with Mental Disease, Arch. Neurol. & Psychiat. **64**:516, 1950.

39. Grunebaum, H., and Altschule, M. D.: Sodium Concentration of Thermal Sweat in Treated and Untreated Patients with Mental Disease, Arch. Neurol. & Psychiat. **63**:444, 1950.

40. Graham, B. F., and Cleghorn, R. A.: Changes in the Circulating Leucocytes Following Electrically Induced Convulsions in Man, J. Clin. Endocrinol. **11**:1469, 1951.

41. Michael, S. T., and Brown, W. T.: Blood Lymphocytes and Adrenal Function in Electric Convulsive Therapy of Psychoses, J. Nerv. & Ment. Dis. **113**:538, 1951.

42. Taylor, R. H.; Gross, M., and Ruby, I. J.: Nonconvulsive Electrostimulation and the Pituitary-Adrenocortical System, J. Nerv. & Ment. Dis. **114**:377, 1951.

43. Gottfried, S. P., and Minsky, I.: Studies on Excretion of Total Neutral 17-Ketosteroids in Schizophrenic Patients, A. M. A. Arch. Neurol. & Psychiat. **66**:708, 1951.

44. Shattock, F. M., and Micklem, L. P.: An Investigation of the Adrenal Cortex Response of Mental Patients to E.C.T. and Insulin Hypoglycaemia, J. Ment. Sc. **98**:287, 1952.

45. Stern, K.; Askonas, B. A., and Cullen, A. M.: Influence of Electroconvulsive Treatment, on Blood Sugar, Total Number of Leucocytes, and Lymphocytes, Am. J. Psychiat. **105**:585, 1949.

in 1949; Cleghorn and Graham,[9] in 1950; Hoagland, Callaway, Elmadjian, and Pincus,[46] in 1950; Tsai, Bennett, May and Gregory,[47] in 1950, and Raskin, Howard, and Singer, in 1951.[48]

PRESENT INVESTIGATION

This paper is presented not as a definitive study of the problem but, rather, as an accumulation of information in a specific area. This limitation of aims was influenced by several factors. An important one of these was my conviction concerning the intrinsic limitations of scientific investigation.

The facts brought forth here, or in any other single study, will not in themselves provide conclusive answers. They must be pooled together with facts obtained from many other such studies. No one investigator, no one laboratory, can produce complete illumination. It is accomplished only after many studies are assembled together and the combined effect of these is determined. Understanding is brought forth for us by the philosophers of science, not by the technicians. Total consideration of many accumulations of data will be needed before this difficulty concerning the schizophrenic patient's pituitary-adrenal cortex activity is resolved.

Technique.—In this study the test utilizing the eosinopenic effect of epinephrine was used for determining adrenal cortex reactivity. This test is dependent on the fact that epinephrine acts as a stimulator of the pituitary-adrenal cortex system. This stimulation is reflected in a decrease in the total circulating eosinophiles of the blood. The eosinophile decrease reaches its maximum point about four hours after the epinephrine has been administered, and the varying degrees of the decrease have been taken to indicate varying degrees of adrenal cortex activity. Many studies of this test have been made in the past,[49] and, although definite objections to it have been discovered, it was considered to be the most satisfactory method for my purpose.

46. Hoagland, H.; Callaway, E.; Elmadjian, F., and Pincus, G.: Adrenal Cortical Responsivity of Psychotic Patients in Relation to Electroshock Treatments, Psychosom. Med. **12**:73, 1950.

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49. (*a*) Laragh, J. H., and Almy, T. P.: Changes in Circulating Eosinophils in Man Following Epinephrine, Insulin, and Surgical Operations, Proc. Soc. Exper. Biol. & Med. **69**:499, 1948. (*b*) Recant, L.; Hume, D. M.; Forsham, P. H., and Thorn, G. W.: Studies on the Effect of Epinephrine on the Pituitary-Adrenocortical System, J. Clin. Endocrinol. **10**:187, 1950. (*c*) Marlow, A. N., and Kallsen, R. A.: Eosinophile and Uric Acid Changes After Epinephrine and Adrenocorticotropic Hormone in Normal Patients and in Adrenal Cortical Insufficiency, Am. J. Med. **8**:534, 1950. (*d*) Samuels, A. J.; Hecht, H. H.; Tyler, F., and Carlisle, R.: Leucocyte Changes Following Intramuscular Injection of Epinephrine and Epinephrine Congeners with Observations on the Alterations Induced by Adrenergic Blocking Agents, ibid. **8**:533, 1950. (*e*) Pellegrino, P. C.; Morris, G. M., and Trubowitz, S.: Eosinophil Response to Epinephrine and Nor-Epinephrine, Proc. Soc. Exper. Biol. & Med. **74**:330, 1950. (*f*) Madison, L. L.: Comparison of the Anterior Pituitary-Adrenal Cortical Stimulating Effect of U.S.P. Epinephrine, Synthetic L-Epinephrine, and Nor-Epinephrine, J. Clin. Invest. **29**:789, 1950. (*g*) Humphreys, R. J., and Raab, W.: Response of Circulating Eosinophils to Nor-Epinephrine, Epinephrine, and Emotional Stress in Humans, Proc. Soc. Exper. Biol. & Med. **74**:302, 1950. (*h*) Posey, E. L., Jr.; Mathieson, D. R.; Mason, H. L., and Bargen, J. A.: The Epinephrine Test for Cortico-Adrenal Reserve Function and the Excretions of Corticosteroids and 17-Ketosteroids in Chronic Ulcerative Colitis, Am. J. M. Sc. **219**:651, 1950. (*i*) Bliss, E. L.; Rubin, S., and Gilbert, T.: Effect

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According to the usual procedure of this test, 0.3 mg. of epinephrine hydrochloride (1 : 1,000) solution was injected subcutaneously into each patient immediately after a specimen of venous blood had been taken for initial eosinophile counts. Then, three to four hours later, another specimen of venous blood was drawn from each patient for eosinophile counts. To determine the extent of the epinephrine activation, the changes in the eosinophile totals from the preepinephrine to the postepinephrine count were ascertained and expressed in percentages of the initial pre-epinephrine count. Eosinophile counts were done as suggested by Randolph[50] in the clinical laboratory of the Palo Alto Veterans Administration Hospital. Statistical analysis of the use of the counting method in this laboratory revealed satisfactory reliability.

The subject group was divided into several subgroups. Most of the patients were men who had been suffering with schizophrenia for from 3 to 34 years. All the conventional subtypes of the schizophrenic reaction were represented, and in all cases the diagnosis had been arrived at and substantiated by several psychiatrists. The patients were all male veterans, of ages ranging from 26 to 64. They were all in relatively good physical condition. An attempt was made to screen out those patients with intercurrent chronic physical illnesses.

In this study, 62 subjects were studied and 64 epinephrine tests were done. These subjects were divided into the following subgroups: Subgroup A consisted of 19 persons to whom was administered 0.3 mg. of epinephrine hydrochloride without any associated limitation of their diet or activities; Subgroup B consisted of 6 subjects to whom was administered 0.5 mg. of epinephrine hydrochloride without any associated limitation of their diet or activities; Subgroup C consisted of 15 subjects to whom was administered 0.3 mg. of epinephrine, and who fasted from 9 p. m. of the evening before the test until the completion of the test and who remained in bed throughout the test period. All patients in these three subgroups had been hospitalized up to the time of testing for periods exceeding six months. Subgroup D consisted of 13 subjects to whom was also adminstered 0.3 mg. epinephrine hydrochloride without limitation of diet or activity but who had recently been readmitted to the hospital. All these 13 patients had chronic schizophrenia but had previously been well enough to leave the hospital for varying lengths of time. They had all been readmitted from one to seven days prior to testing because of difficulty with their illness. It should be pointed out that this subgroup included persons who frequently had marked anxiety symptoms and were more physically debilitated than members of the other subgroups, who had been more settled and better cared for (during their prolonged hospitalizations). Subgroup E consisted of five subjects to whom was administered 0.3 mg. of epinephrine without limitation of diet or activity but who were receiving a course of electroshock therapy at the time. These patients, again, had all been hospitalized for more than six months prior to being tested.

Several subgroups were set up for study of the internal validity of the experiment. Subgroup F consisted of six subjects taken from Subgroup A to whom was readministered (after

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of Adrenalin on Adrenal Cortical Function, J. Clin. Endocrinol. **11**:46, 1951. (*j*) Turner, F. P.: Eosinophile Responses to Epinephrine and ACTH in Peptic Ulcer, Gastroenterology **18**:419, 1951. (*k*) Ferguson, J. H.: Experiences with ACTH and Eosinophil Counts in Normal Pregnancy and Toxemia, Am. J. Obst. & Gynec. **61**:603, 1951. (*l*) Best, W. R., and Samter, M.: Variation and Error in Eosinophil Counts of Blood and Bone Marrow, Blood **6**:61, 1951. (*m*) Best, W. R., Muehrcke, R. C., and Kark, R. M.: Studies on Adrenocortical Eosinopenia; abstracted, J. Clin. Invest. **30**:629, 1951; (*n*) Clinical and Statistical Evaluation of 4-Hour Eosinophil Response Tests, J. Lab. & Clin. Med. **38**:790, 1951; (*o*) Studies on Adrenocortical Eosinopenia, J. Clin. Invest. **31**:733, 1952. (*p*) Dowden, C. W., and Bradbury, J. T.: Eosinophil Response to Epinephrine and Corticotropin: Studies in Alcoholics and Nonalcoholics, J. A. M. A. **149**:725, 1952. (*q*) Fisher, B., and Fisher, E. R.: Observations on the Eosinophil Count in Man: Proposed Test of Adrenal Cortical Function, Am. J. M. Sc. **221**:121, 1951. (*r*) Best, W. R.; Kark, R. M.; Muehrcke, R. C., and Samter, M.: Clinical Value of Eosinophil Counts and Eosinophil Response Tests, J. A. M. A. **151**:702, 1953.

50. Randolph, T. G.: Differentiation and Enumeration of Eosinophils in the Counting Chamber with a Glycol Stain: Valuable Technique in Appraising ACTH Dosage, J. Lab. & Clin. Med. **34**:1696, 1949.

three to four weeks) the 0.3 mg. of epinephrine without limitations on diet or activity. Subgroup G consisted of 11 subjects taken from Subgroup A who were checked for the 8 a.m.-to-noon eosinophile change without the influence of epinephrine injection. With these patients, the two venous blood specimens were drawn and the eosinophile counts were done, but no epinephrine was injected. Another subgroup—Subgroup H—was put through the same routine. However, the four subjects in this subgroup were not taken from Subgroup A but were, like those in Subgroup E, patients currently receiving electroshock therapy.

In addition to these studies, a limited investigation of the eosinophile responses to convulsive and subconvulsive types of electroshock therapy was made. Specimens of venous blood were drawn from patients immediately before and three to four hours after their respective treatments. Food was withheld from 9 p. m. of the evening before the treatment until after the second blood specimen was drawn. No limitation of activity was imposed, however. Involved in

TABLE 1.—*Range of Percentage Decreases in Eosinophile Count*

Subgroups	Percentage Decreases	Range of Percentage Decreases
A (19)	22; 24; 43; 24; 54; 78; 47; 39; 58; 58; 46; 45; +1; 49; 51; 43; 47; 74; 79	+1 to −79
B (6)	52; 58; 58; 52; 60; 50	−50 to −60
C (15)	49; 40; 62; 53; 40; 23; 34; 47; 32; 46; 27; 47; 60; 41; 16	−16 to −62
D (13)	52; 0; 40; 30; 62; 52; 85; 50; 49; 11; 30; +8; +117	+117 to −62
E (5)	51; 50; 23; 14; 40	−14 to −51
F (6)	46; 40; 45; 43; 68; 35	−33 to −68
G (11)	28; 4; 6; 35; 33; 16; 13; 26; 10; +22; +34	+34 to −35
H (4)	57; 43; 54; 31; 6; 33	−6 to −57
Convulsive electroshock therapy	71; 55; 26; 60; 42; +11; 71; +17; 35; 39; 37; 20; 54; 55; +127; 33; 23; 0; 57; 33; 43; 64; 46; +13; 0; 42; 9; 60; 37; 60; 54; 82; 46; 27; 0; 61; +84; 0; 99; 24; +5; 55; 14	+127 to −82
Subconvulsive	24; 8; 31; 6; 34; 30; 44; 30; 53; 60; 44; 20; 20; 7; 43; +8; 35; 49; 27; 41; 58; 88; +17; +22; 25; 44; 11	+22 to −88

TABLE 2.—*Arithmetical Means, Standard Deviations, and Standard Errors for Each Subgroup*

									Electroshock Therapy	
Subgroups	A	B	C	D	E	F	G	H	Convulsive	Subconvulsive
Means	−46	−55	−41	−31	−36	−46	−16	−27	−29	−30
Standard deviations	±21	±4	±13	±47	±15	±11	±22	±34	±42	±23
Standard errors	±4.8	±1.6	±3.4	±13.0	±6.7	±4.5	±6.6	±13.9	±6.4	±4.4

this investigation were 16 patients taking the convulsive types of electroshock treatments and 10 patients taking the subconvulsive type. In order that the extent of the electrotherapy activation might be determined, the changes between the pretreatment and the post-treatment eosinophile counts were expressed in percentages of the pretreatment eosinophile count.

Results.—The arithmetical mean of 70 pretest eosinophile counts of the patients not currently receiving electrotherapy was derived. This mean was 195 cells per cubic millimeter. This figure compares favorably with the mean of 197 cells per cubic millimeter for 14 schizophrenic patients, as derived by Rud,[51] and the means of 193 cells per cubic millimeter in (1950) and 214 cells per cubic millimeter (in 1951) for 29 and 28 schizophrenic patients, respectively, as derived by Hiatt, Rothwell, and Horwitt.[20]

51. Rud, F.: The Eosinophil Count in Health and in Mental Disease: Biometrical Study, Acta psychiat. & neurol., supp. 40, 1947.

If the initial eosinophile counts for the 13 patients of Subgroup D are not included in the calculation, the mean for the other patients was 201 cells per cubic millimeter. The mean for the patients of Subgroup D was 171 cells per cubic millimeter. This separation was made because the patients of Subgroup D were different from those of the other subgroups in that they had recently been out of the hospital environment, whereas all the others had been hospitalized up to the testing time for periods exceeding six months. The mean for 102 initial counts for patients currently receiving electrotherapy was figured at 243 cells per cubic millimeter.

The four-hour percentage decrease from the pretest eosinophile count was calculated for each sample. The extreme range of these decreases was determined for each subgroup (Table 1).

Arithmetical means, standard deviations, and standard errors of the arithmetical means were calculated for each subgroup (Table 2).

Also, standard errors of the differences in the arithmetical means for various subgroups were determined. (The use of this procedure will become apparent in the "Comment" section.) These values are listed in Table 3.

TABLE 3.—*Standard Errors of Arithmetical Means for Various Subgroups*

Subgroups	A	B	C	D	E	F	G	H	Convulsive Electroshock Therapy
A	....	....	....	....	....	....	....	....	....
B	5.1	....	....	....	....	....	....	....	....
C	5.9	3.8	....	....	....	....	....	....	....
D	13.9	13.1	13.4	....	....	....	....	....	....
E	8.2	6.9	7.5	14.6	....	....	....	....	....
F	6.6	4.8	5.6	13.7	8.1	....	....	....	....
G	8.2	6.8	7.4	14.6	9.4	8	....	....	....
H	14.7	14	14	19	15.4	14.6	15.4	....	....
Convulsive electroshock therapy	8	6.6	7.2	14.5	9.3	7.8	9.2	15.3	....
Subconvulsive electroshock therapy	6.5	4.7	5.6	13.7	8	6.3	7.9	14.6	7.8

COMMENT

Consideration of the pretest eosinophile counts was taken up primarily with the purpose of establishing, with respect to eosinophile levels, the similarity of this particular population of schizophrenic patients to other such populations. This assumption of similarity seems justified.

In determining the arithmetical mean for pretest eosinophile counts, no distinction was made between fasting and nonfasting patients. It has been demonstrated by others [52] that this factor is of little significance.

The arithmetical mean for "resting" or "pretest" eosinophile counts of so-called normal persons has been calculated by various observers at different levels. Some of these means are cited: 181 and 146 cells [49b]; 250 cells [49l]; 147 cells [49k]; 221 and 180 cells [49q]; 163 cells [51]; 149 cells [53]; 140 cells [54]; 170 cells,[55] and 157 cells,[56] per

52. Fisher and Fisher.[49q] Rud.[51]

53. Gabrilove, J. L.: The Level of the Circulating Eosinophils Following Trauma, J. Clin. Endocrinol. **10**:637, 1950.

54. Kuhl, W. J.; Wilson, H., and Ralli, E. P.: Measurements of Adrenal Cortical Activity in Young Men Subjected to Acute Stress, J. Clin. Endocrinol. **12**:393, 1952.

(Footnote continued on next page)

cubic millimeter. It is apparent that most of these levels are lower than the means calculated for schizophrenic patients. This fact was also pointed out in Rud's [51] work; however, its significance remains obscure.

When the plans for this project were first drawn up, it was felt important to consider a factor which has been neglected in some other studies. As several investigators have pointed out,[57] a decrease in the eosinophile level can result from influences other than the injection of a specific activating agent. The normal diurnal variation of the eosinophile level has been described. Also, some studies have been made of the effect of placebo injections on the eosinophile level. It was with these factors in mind that Subgroup G was set up.

As stated before, no specific activator—i. e., epinephrine—was injected into patients comprising Subgroup G. Even so, a mean four-hour eosinophile decrease of 10% was recorded. The mean four-hour eosinophile decrease after injection of 0.3 mg. of epinephrine hydrochloride (Subgroup A) was 46%. The difference between these two means was calculated to be statistically significant to the degree of $P < 0.01$ by the use of standard errors and the t table. Therefore, although there is a consistent, nonspecific difference between eosinophile counts at 8 a. m. and at noon, this difference does not invalidate the significance of the greater eosinophile decrease after injection of epinephrine.

This finding of a nonspecific four-hour decrease of 10% is similar to that reported by Fisher and Fisher.[49q] They found in 46 normal control subjects a mean decrease of 10% between 8 a. m. and noon. Rud [51] found a decrease of 7.6% in the large series of normal subjects he studied. A mean change from 8 a. m. to noon of approximately +1% was calculated from tables found in Bonner's study of 99 normal controls.[57i] In reporting a study of nine controls, Kullander [57j] gave a mean decrease from 8 a. m. to noon of 17%.

In other studies, the effect of the experimental manipulations per se has been investigated by determining the eosinophile-changing effect of placebo injections. Best, and Kark and Muehrcke [49m] have presented a report of placebo injections producing an 8 a. m.-to-noon mean eosinophile decrease of 20%. Another study by the same investigators,[49n] which involved a larger group of subjects, was reported as resulting in a placebo-effected 8 a. m.-to-noon mean decrease of 10%. Madison [49f] discovered a placebo-induced 8 a. m.-to-noon mean decrease of 8% for his group of control subjects. An 8 a. m.-to-noon mean decrease of 10.7% was reported by Dowden and Bradbury [49p] from their study of the effect of placebo injection on 45 control subjects.

55. Hills, A. G.; Forsham, P. H., and Finch, C. A.: Changes in Circulating Leukocytes Induced by Pituitary Adrenocorticotropic Hormone (ACTH) in Man, J. Clin. Endocrinol. **7**:458, 1947.

56. Shands, H. C., and Bartter, F. C.: A Statistical Analysis of the "ACTH Test" Changes in Eosinophil Count in Normal and in Psychoneurotic Subjects, J. Clin. Endocrinol. **12**:178, 1952.

57. (*a*) Recant, Hume, Forsham, and Thorn. [49b] (*b*) Madison. [49f] (*c*) Best and Samter. [49l] (*d*) Best, Muehrcke, and Kark.[49m, n] (*e*) Fisher and Fisher.[49q] (*f*) Rud.[51] (*h*) Swanson, J. N.: Practical Importance of the Diurnal Variation in Number of the Circulating Eosinophils, J. Clin. Invest. **30**:677, 1951. (*i*) Bonner, C. D.: Eosinophil Levels as an Index of Adrenal Responsiveness: Factors that Affect Value of Eosinophil Counts, J. A. M. A. **148**:634, 1952. (*j*) Kullander, S.: Studies on Eosinophil Leucocytes in Pregnancy, Acta endocrinol. **10**:135, 1952.

From a review of these findings of various investigators, it becomes apparent that there is a definite similarity between the nonspecific diurnal eosinophile variation of the schizophrenic patients studied by this project and that of normal control subjects studied by other investigators. Because of the similarity between the nonspecific diurnal variation of eosinophiles in all subjects and the eosinophile decrease supposedly induced by placebo injection, it is probable that the placebo injection, i. e., experimental manipulation, produces only insignificantly small effects on the eosinophile level.

The injection of 0.3 mg. of epinephrine subcutaneously in the patients of Subgroup A resulted in a mean four-hour eosinophile decrease of 46%. An attempt to reproduce this result, and so test its consistency—the attempt is represented by Subgroup F—also resulted in a mean decrease of 46%. As has been shown above, the difference between these epinephrine-induced decreases and other, nonspecific, eosinophile decreases is of considerable significance.

Other investigators have reported the results of the tests with 0.3 mg. of epinephrine in various groups of nonschizophrenic persons. The findings of these

TABLE 4.—*Results of Epinephrine Tests of Various Investigators*

Authors	Mean Four-Hour Decrease, %	Standard Deviation
Recant, Hume, Forsham and Thorn [49b]	62	± 9.6
Madison [49f]	55	±11.4
Ferguson [49k]	54	±18.5
Dowden and Bradbury [49p]	49	±18.4
Fisher and Fisher [49q]	43	±24

investigations are summarized in Table 4. A number of other studies have been reported, but the epinephrine doses varied from that of 0.3 mg., and therefore the results are not comparable.

A statistical analysis, using the method of standard errors and the *t* table, reveals that the difference between the mean four-hour decrease for Subgroup A in this study and the mean four-hour decreases in the other five studies cited above is of significance in only one instance. In other words, the difference between the mean four-hour decrease for Subgroup A and the mean four-hour decreases of all the other studies, except that of Recant, Hume, Forsham, and Thorn, can probably be attributed to random errors of sampling. There is, then, a poor statistical basis for the hypothetical statement that the eosinopenic responses of the schizophrenic patients in this study were impaired as compared with those of "normal, control" subjects. This information tends to support the contention that pituitary-adrenal cortex reactivity is not decreased in schizophrenia.

In several studies [7] it has been presented that in a group of schizophrenic patients a certain proportion of the total number of patients will demonstrate impaired pituitary-adrenal cortex reactivity. It could be pointed out that, in the 19 epinephrine tests of Subgroup A and the 6 tests of Subgroup F, there were 7 in which the patient reacted with less than a 40% eosinophile decrease. It is not felt, however, that these seven instances of apparently impaired response represent a pathologic condition of the pituitary-adrenal cortex system. A number of investigators have emphasized

the occurrence of "false-negative" responses in tests of the system reactivity.[58] For this reason, any interpretations or conclusions about individual test results have studiously been avoided. In any group, schizophrenic or control, a certain proportion of the subjects will respond to reactivity tests in a manner suggesting impaired function of the pituitary-adrenal cortex system. The conviction that this apparent impairment does not represent a pathologic change is just as valid for the schizophrenic subjects as it is for the controls.

Subgroup C represented an extension of the investigation carried on in Subgroup A, with the added factor that the subjects were on a regimen of fasting and bed rest. The mean four-hour decrease in eosinophiles for this subgroup was 41%. The difference between this mean and the mean four-hour decrease for Subgroup A (46%) is of little statistical significance (standard errors and t table method). This fact of similarity conforms to the impression gained by others [52] in work with normal controls, i. e., that fasting and bed-rest regimens have little effect in these studies.

Another resemblance of this schizophrenic population to the "normal" population is found in the results of the tests in Subgroup B. Recant, Hume, Forsham, and Thorn [49b] pointed out that doses of epinephrine larger than 0.3 mg. in the four-hour tests produced an exaggerated reaction and a "loss of specificity." Use of 0.5 mg. of epinephrine in two studies [59] resulted in mean four-hour decreases of 56 and 58%, respectively. The mean four-hour decrease for Subgroup B was 55%. Also, the standard deviation for the test results in this subgroup was smaller than for any others of the patient subgroups. All the eosinophile decreases ranged from 50 to 60% —a fact that is in agreement with the statement about the exaggerated effects of epinephrine doses larger than 0.3 mg.

Whereas the results obtained in the previously discussed subgroups seem rather uncomplicated, the results of the tests administered to patients of Subgroup D, E, and H are more difficult to understand. The mean four-hour decrease for Subgroup D was 31%, and the standard deviation was very high. Statistical analysis of the difference between the means for Subgroups D and A reveals little significance. The difference between the means for Subgroups D and G is of a higher order of significance ($P = 0.1$). It can be concluded that epinephrine did produce a specific result.

A similar situation occurred with Subgroup E. The difference between the mean four-hour decreases of Subgroups E and A is of poor statistical significance. The difference between the means for Subgroups E and G is of strong significance ($P = 0.02$). The epinephrine test here also appears to have had a specific effect. However, a difference existed between the means for Subgroups D and E in that the standard deviation for Subgroup E was much smaller than that for Subgroup D. Subgroup E, apparently, was a more homogeneous population than Subgroup D.

In setting up these two subgroups, it was evident that factors other than epinephrine activation of the pituitary-adrenal cortex system were at work. As has been mentioned previously, the patients of Subgroup D were in a much more unstable

58. Hiatt, Rothwell, and Horwitt.[20] Recant, Hume, Forsham, and Thorn.[49b] Best and Samter. [49l] Best, Muehrcke, and Kark. [49m-o] Fisher and Fisher. [49q] Eosinophils as Indicators, Annotation, Brit. M. J. **2**:224, 1951. Krupp, M. A.; Saier, M.; Keddie, P.; Tanner, R., and Snell, A. M.: Experience with Cortisone and ACTH in a Private Clinic, California Med. **75**:6, 1951.

59. Laragh and Almy. [49a] Posey and others. [49b]

state of their illness than those of Subgroup A, B, and C. They presented more overt anxiety; more stress was apparent. The patients of Subgroup E were receiving a course of electroshock therapy at the time of the epinephrine testing.

Several authors have pointed out the wide range of stresses that can stimulate the pituitary-adrenal cortex system.[60] A number of studies have been made relative to the relationship between emotional stress (or anxiety) and pituitary-adrenal cortex activation.[61] It might be suggested that such stress mechanisms were active in patients of Subgroup D and that variable degrees of refractoriness to further activation existed in these persons. The uncontrolled variability of this factor could be considered to be a cause of the large standard deviation of the epinephrine test results.

Many investigations have revealed the stimulating effects of electroshock therapy on the pituitary-adrenal cortex system.[62] These effects were presumably active in patients of Subgroup E, and a relative refractoriness to further stimulation could, similarly, be assumed to be present in these persons. However, the variability in the electroshock effect should be considerably less than that of the effect of emotional stress. This decreased variability may be reflected in the decreased magnitude of the standard deviation for the test results of Subgroup E, as compared with the standard deviation for the test results in Subgroup D.

Such possibilities are speculative, however, and not actually within the scope of the present paper. It can only be said with certainty that such stress factors—strong emotional stress, electroshock therapy—are of definite influence and must be taken into consideration in any such testing. This conclusion is supported by the evidence offered in Subgroup H. The standard deviation for this group—unstimulated by epinephrine but undergoing a course of electroshock treatments—was quite large, indicating a variable influence at work on the pituitary-adrenal cortex system.

The eosinophile-decreasing effects of convulsive and subconvulsive electroshock therapy were compared. The mean four-hour decreases were very similar. The standard deviation for the group receiving convulsive therapy was much larger than that for the group receiving subconvulsive therapy. The difference between the mean four-hour decreases for these two groups and the mean decrease for Subgroup A is of strong statistical significance ($P < 0.05$). Also, the difference between these two mean decreases and the decrease for Subgroup G is of strong statistical significance ($P < 0.02$). It can be concluded, therefore, that the therapy had produced a specific effect on the pituitary-adrenal cortex system. Although it would appear that this effect was not as strong as the effect of epinephrine, the factor of refractoriness of the system with repeated stimulation may have entered in here.

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60. Selye, H.: General Adaptation Syndrome and Diseases of Adaptation, Am. J. Med. **10**:549, 1951. Sayers, G.: Regulation of Secretory Activity of Adrenal Cortex, ibid. **10**:539, 1951.

61. Humphreys and Raab.[49g] Campbell, R. B.; Cleghorn, R. A.; Elliott, F. H.; Graham, B. F.; Rublee, N. K., and Saffran, M.: Anxiety States: Their Response to ACTH and to Isotonic Saline, Proceedings of First Clinical ACTH Conference, edited by J. R. Mote, Philadelphia, The Blakiston Company, 1950, p. 561. Shands, H. C., and Finesinger, J. B.: Lymphocytes in the Psychoneuroses: Preliminary Observations, Am. J. Psychiat. **105**:277, 1948. Renold, A. E.; Quigley, T. B.; Kennard, H. E., and Thorn, G. W.: Reaction of the Adrenal Cortex to Physical and Emotional Stress in College Oarsmen, New England J. Med. **244**:754, 1951.

62. Ashby.[11] Footnotes 29 to 41.

SUMMARY

A review of the controversy about the reactivity of the pituitary-adrenal cortex system in schizophrenic patients is presented.

The project reported here—set up for statistical evaluation of this reactivity—is outlined.

The results of this investigation would tend to add weight to the conclusion that the reactivity is not impaired in schizophrenia.

It is confirmed that a number of nonspecific stress factors influence the level of pituitary-adrenal cortex activity.

The presence of false-negative responses in any evaluation of the pituitary-adrenal cortex system is emphasized.

Fasting and bed rest do not appear to have an important influence on the activity of this system.

Epinephrine in large doses loses its specificity.

Speculation about the refractoriness of the pituitary-adrenal cortex system is offered.

Electroshock therapy, both convulsive and subconvulsive, exercises a specific influence on the pituitary-adrenal cortex system.

Relative eosinophilia in schizophrenic patients was again found in this population, as has been reported by other authors.

CENTRAL INHIBITION IN CORTICAL CONDITIONED REFLEXES

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IN THE NORMAL electroencephalogram the alpha potential is a fairly regular 8- to 13-cps rhythm, which is best obtained from the occipital leads and is most prominent in the waking, but resting, state. It is normally promptly suppressed by visual attention, such as is produced by flashing a light in the subject's eyes. It can also be blocked by any sufficiently forceful stimulus requiring alertness and attentiveness, such as a loud sound or the solving of a difficult mathematical problem. However, except for these forceful stimuli, the blocking of the alpha potential is fairly specific for visual effects and does not normally respond, for example, to sounds of low intensity. Therefore, at least within a certain range of intensity, the alpha blocking to visual stimuli is a specific inborn, or unconditioned, response.

Study of the conditioned alpha rhythm in man began in 1936, when Loomis, Harvey, and Hobart,[1] as part of a more extensive study of brain potentials in normal subjects, noted that a low-tone stimulus lasting five seconds had no initial effect on alpha activity. But when presented several times in succession together with a light stimulus, the tone acquired the ability to suppress alpha activity when it was applied alone. They also noted that this conditioned response was rapidly extinguished when not reinforced by the light, e. g., the unconditioned stimulus. This work was elaborated by Travis and Egan [2] in 1938; Knott and Henry,[3] in 1941, and, finally, Jasper and Shagass [4] worked out in detail the various forms of conditioning of the alpha rhythm and were able to demonstrate many of the laws of conditioned reflex activity.

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† Dr. Ross died Aug. 22, 1952.

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This study was originally planned together with Dr. Ross (formerly resident, Division of Pulmonary Diseases, Montefiore Hospital), who died before the work could be completed.

1. Loomis, A. L.; Harvey, E. N., and Hobart, G.: Electrical Potentials of the Human Brain, J. Exper. Psychol. **19**:249, 1936.

2. Travis, L. E., and Egan, J. P.: Conditioning of the Electrical Response of the Cortex, J. Exper. Psychol. **22**:524, 1938.

3. Knott, J. R., and Henry, C. E.: Conditioning of the Blocking of the Alpha Rhythm of the Human Electroencephalogram, J. Exper. Psychol. **28**:134, 1941.

4. Jasper, H., and Shagass, C.: Conditioning the Occipital Alpha Rhythm in Man, J. Exper. Psychol. **28**:373, 1941.

More recently, Motokawa and Huzimori [5] and Iwama [6] established similar conditioned reflexes and felt they could correlate the degree of inhibitory activity with alpha facilitation.

The substance of all this work was that the alpha rhythm could be conditioned and that it was subject to the same laws of conditioning as any other physiological process

According to classic Pavlovian [7] theory, the establishment of conditioned reflexes requires the setting up of temporary physiological connections, or links, between various areas of the cortex. For example, when Pavlov conditioned the salivary response to a bell, using the inborn response to food as an unconditioned stimulus, this required that a connection be established between the "food center" (whether this be localized or diffuse is unimportant for our purpose) and the auditory "analyzer," or receiving area. Pavlov assumed that the constant association of the bell with food resulted in the irradiation of an excitatory process from one center to another, establishing a more or less stable connection. When the conditioned response was extinguished by repeatedly presenting the bell without the food, Pavlov assumed that an inhibitory process had prevented or impaired the irradiation of the original excitation. That the temporary connection was not severed, but only damped or inhibited, is shown by the fact that the reflex is spontaneously restored if a sufficient time interval is allowed after extinction has taken place. It requires many such extinctions over a long period of time to dissolve the connection so that it no longer spontaneously restores itself.

We decided to put these hypotheses to the experimental test and, in particular, with the graphic aid of the electroencephalgram, to investigate the development, spread, and resolution of the inhibitory process.

PROBLEM OF METHODOLOGY

In order to measure the nature and strength of the induced cerebral activity, one needs a quantitative indicator of the spread of electrical impulses, preferably two indicators—(1) the graphic demonstration in cortical tracings of the passage of the impulse, and (2) a measurement of the rate of transmission of the impulse.

Subjects were instructed to respond by pressing a key as rapidly as possible each time the light was flashed. The key broke a circuit, which caused a deflection of the pen on a standard ink-writing oscillograph. The light stimulus was recorded on the same paper through a photoelectric cell with suitable amplifiers, and ordinary scalp electrodes were applied to the occipital and precentral regions for simultaneous recording of the appropriate brain waves. Thus, the time taken from the onset of the light to the depression of the key could be accurately measured. This, we assumed, was a measure of the time taken by an impulse traveling from the visual receiving area to the motor strip, plus, of course, the time from onset of light to arrival in the visual cortex and from arrival in the motor area to break in the circuit. The latter two delay times should be constant, so that any alteration in the visuomotor reaction time is probably a result of alteration in cortical transmission time.

5. Motokawa, K., and Huzimori, B.: Electroencephalograms and Conditioned Reflexes, Tohoku J. Exper. Med. **50**:215, 1949.

6. Iwama, K.: Delayed Conditioned Reflex in Man and Brain Waves, Tohoku J. Exper. Med. **52**:53, 1950.

7. Pavlov, I. P.: Lectures on Conditioned Reflexes: Twenty-Five Years of Objective Study of the Higher Nervous Activity (Behavior) of Animals, translated and edited by W. H. Gantt, New York, International Publishers, 1928.

At the same time, in the characteristic "blocking" of the alpha rhythm one has another indicator of the arrival of the light stimulus in the central nervous system.

We, therefore, established, by voluntary instruction, a temporary connection between the visual receiving area and the motor cortex, and could measure the rate of transmission between these areas, as well as demonstrate graphically the central arrival of the light stimulus.

The normal visuomotor reaction time has been measured by many workers, including Monnier [8] and Stamm,[9] and has been found to be a relatively constant figure of the order of 200 to 300 msec.

The visuomotor reaction time, then, provides one with a measurement of central conduction time, which is linked with the unconditioned stimulus in the conditioned reflex system. The visuomotor reaction also represents a temporary connection, which, if the Pavlovian hypothesis is correct, is based on the irradiation of an excitatory process from one cortical area to another. If this is so, it should be possible, by inducing an inhibitory process in the same system, to pro-

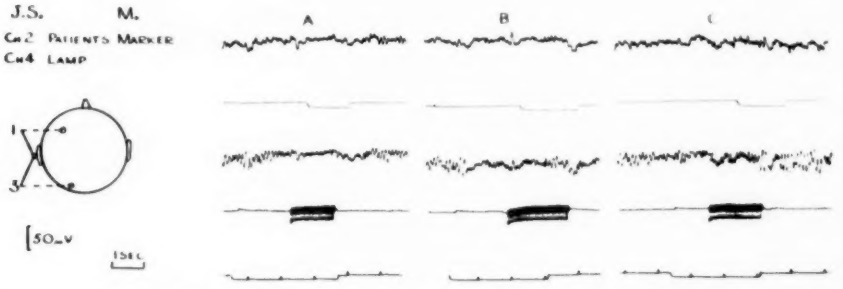

Fig. 1.—Initial conditioning of alpha rhythm and visuomotor reaction time following extinction.

long the visuomotor reaction time, e. g., to demonstrate a delay in cortical conduction.

It was noted before that, according to Pavlov, the extinction of a conditioned reflex involves the setting up of an inhibitory process. By noting a change in the visuomotor reaction time, one can estimate the nature and the extent of the physiological process involved in extinguishing the conditioned alpha rhythm.

PRESENT STUDY

Experiment.—The experiment was carried out as follows: In six normal subjects we established a conditioned alpha blocking to a low-pitched sound stimulus. That is, after we had paired a sound stimulus, which at first had no effect on the alpha rhythm, with a flickered light (the unconditioned stimulus), the alpha rhythm was, as it were, taught or conditioned to respond to sound alone. At the same time, in the same brain, by our instructing the subject to respond to the light stimulus by pressing a key, the visuomotor system was linked to the unconditioned stimulus in the conditioned reflex system. Therefore each time the conditioned reflex was reinforced, we obtained a measurement of cortical conduction time.

8. Monnier, M.: Mesure de la durée d'un processus d'intégration corticale: temps d'intégration opto-motrice chez l'homme, Helv. physiol. et pharmacol. Acta **7**:52, 1949.

9. Stamm, J. S.: On Relationship Between Reaction Time to Light and Latency of Blocking of the Alpha Rhythm, Electroencephalog. & Clin. Neurophysiol. **4**:61, 1952.

Results.—Figure 1 demonstrates the initial conditioning of the alpha rhythm and the visuomotor reaction time following extinction. In *A* the alpha rhythm does not respond to sound. In *B* conditioning is complete, and the alpha rhythm is blocked on sound. Reaction times in *A* and *B* are normal. In *C* the conditioned reflex has been extinguished by nonreinforcement. (Note that the alpha rhythm no longer responds to sound.) If the unconditioned stimulus (light) is then suddenly applied, the visuomotor reaction time is markedly prolonged.

In a protocol of this experiment (Table 1) the figures are presented. The normal reaction time after conditioning was 0.3 sec. After a period of nonrein-

TABLE 1.—*Extinction*

Trial	Stimulus	Latency, Sec.	Comment
14	Buzzer	0.3	Reinforced
15	Buzzer	0.3	Reinforced
16	Buzzer	...	Unreinforced
17	Buzzer	...	Unreinforced
18	Buzzer	...	Unreinforced
19	Buzzer	...	Unreinforced
20	Buzzer	0.6	Reinforced
21	Buzzer	...	Unreinforced
22	Buzzer	...	Unreinforced
23	Buzzer	...	Unreinforced
24	Buzzer	0.8	Reinforced

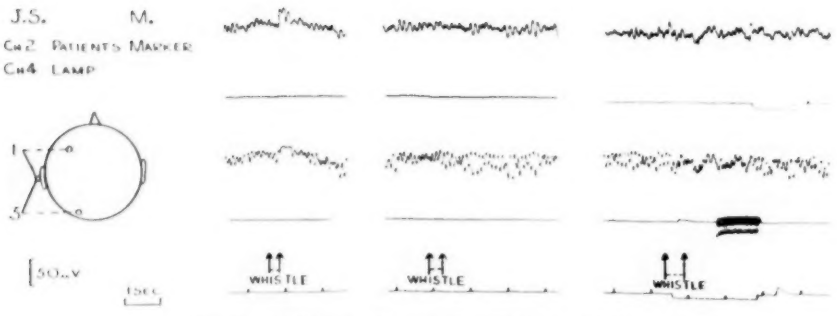

Fig. 2.—Inhibitory influence of conditioned inhibitor.

forcement, during which the alpha rhythm ceased to respond to sound, we again presented the light (reinforced) and noted the prolongation of reaction time to 0.8 sec.

These figures support the Pavlovian hypothesis. Extinction of the conditioned reflex has given rise to a process causing an increase in cortical transmission time.

Extinction, however, was not the only form of central inhibition described by Pavlov. It seemed worth while, in view of these initial findings, to investigate other forms of inhibitory activity in order to confirm and elaborate the evidence.

If one conditions the alpha rhythm to respond to a specific sound and, after the establishment of conditioning, suddenly presents a new extraneous sound, the alpha rhythm will respond to this as well. Pavlov called this "generalization" of the conditioned reflex. But if one constantly reinforces the original sound

stimulus and never reinforces the new sound stimulus, the alpha rhythm, as it were learns to differentiate the two stimuli and responds only to the original one. The response to the second sound stimulus has been extinguished, and it now becomes what Pavlov called a conditioned inhibitor. It exerts an inhibitory influence.

Figure 2 shows these processes. In *A* the alpha rhythm responds to the new stimulus (whistle). In *B* differentiation has occurred, and the alpha activity no longer responds—as a matter of fact, it appears augmented. *C* is the tracing we obtain when the conditioned inhibitor—whistle and the conditioned excitor (buzzer) are applied simultaneously and are followed by the light stimulus. Note that the

TABLE 2.—*Differential Inhibition*

Trial	Stimulus	Visuomotor Latency, Sec	Comment
12	Buzzer	0.3	Reinforced
15	Buzzer	0.3	Reinforced
16	Whistle	...	Unreinforced
17	Buzzer	0.4	Reinforced
18	Whistle	...	Unreinforced
19	Buzzer	0.35	Reinforced
20	Whistle	...	Unreinforced
21	Whistle	...	Unreinforced
22	Buzzer	0.3	Reinforced
23	Whistle } Buzzer }	0.8	Reinforced
24	Whistle } Buzzer }	0.7	Reinforced
25	Buzzer	0.45	Reinforced
26	Buzzer	0.3	Reinforced

TABLE 3.—*Delayed Inhibition*

Trial	Stimulus	Latency, Sec.	Interval, Sec.	Comment
14	Buzzer	0.35	6	Reinforced
15	Buzzer	0.3	6	Reinforced
16	Buzzer	0.45	0.5	Reinforced
18	Buzzer	0.35	6	Reinforced
20	Buzzer	0.3	6	Reinforced
21	Buzzer	0.6	0.5	Reinforced

manual response is considerably delayed, reflecting the influence of the conditioned inhibitor. Table 2 is the protocol of this experiment and illustrates the process of differentiation and, finally, the prolongation of the visuomotor reaction time to 0.8 sec.

A third form of central inhibition is that induced when the time between the conditioned and the unconditioned stimulus is increased. For example, if the conditioned reflex is originally established by presenting the light 0.5 sec. after the onset of the buzzer, the alpha activity "learns" to respond within 0.5 sec. after onset of sound. If, now, one begins to present the light stimulus 6 seconds after onset of sound, the alpha rhythm will gradually cease to respond at 0.5 sec. and the response will be delayed until 6 seconds have elapsed. Some physiological process must suppress the previously established early response of the alpha rhythm. If this process is inhibition and the six seconds following onset of sound is an "inhibitory interval," then a measurement of visuomotor reaction during

that interval should show a delay in cortical conduction. Table 3 illustrates what happens when the light is suddenly flashed during the inhibitory interval after the delayed conditioned reflex has been established. Reaction time is prolonged to 0.6 sec.

Table 4 presents a summary of data. The figures given are average response times under the given circumstances. In each of the three forms of inhibition, the delay in reaction time is statistically significant.[10]

CONCLUSIONS

We have been able to confirm the results of previous workers in showing that the same laws apply to the conditioned alpha rhythm as to other physiological responses. In addition, by use of this technique, we have demonstrated, in three different forms, the existence, and measured the strength, of central inhibitory processes. The findings demonstrate the validity of Pavlov's assumptions regarding the central processes responsible for his experimental results, and the technique provides a means of directly investigating (and influencing) the fundamental physiology of cortical activity.

TABLE 4.—*Summary of Data*

	Mean Visuomotor Latency, in Seconds				
			Inhibition		
Subject	Unconditioned Latency	Conditioned Latency	Delayed	Differential	Extinction
S. T.	0.35	0.3	0.5	0.7	0.8
J. G.	0.3	0.2	0.45	0.6	0.7
M. S.	0.4	0.25	0.5	0.65	0.75
F. M.	0.4	0.3	0.55	0.65	0.8
J. S.	0.45	0.3	0.6	0.7	0.9
K. R.	0.4	0.35	0.65	0.75	0.85

SUMMARY

Within a certain range of intensity the suppression of the normal 8- to 13-cps, or alpha, rhythm to a light stimulus is a specific, inborn, unconditioned response. By successive pairing of a sound stimulus of low intensity with the light stimulus the alpha rhythm can be conditioned to respond to a sound stimulus alone. The establishment and differentiation of conditioned reflexes imply the existence of specific excitatory and inhibitory processes, the magnitude and characteristics of which have never been directly observed. We employ two measurements: (1) the graphic demonstration in electroencephalographic tracings of the origin, course, and spread of the induced electrical activity, and (2) the determinations of the rate of cortical conduction between the occipital and the precentral region.

Three distinct forms of Pavlovian inhibition were established: extinction of conditioned reflex, delayed conditioning, and differential inhibition. The above measurements were made under each of these categories, and our results indicate a significant delay in cortical conduction time whenever the inhibitory process is induced, as demonstrated by the electroencephalogram.

The delay in conduction time indicates the presence, and measures the degree, of the central inhibitory process.

10. A complete statistical study of these and subsequent data will be presented in a forthcoming communication.

STATISTICAL CONTROL STUDIES IN NEUROLOGY

IV. Discomfort with Conjugate Gaze in Head Injuries

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THIS IS the fourth of a series of statistical studies in neurology dealing with the evaluation of clinical signs by comparing their incidence in given groups of cases with adequate controls. In the previous papers we discussed the Babinski, Wilson pronator, and Hoffmann signs.[1]

The present investigation concerns itself with the clinical significance of discomfort with conjugate gaze studied in 2,604 cases of head injury. Mann,[2] in 1931, discussed its occurrence in head injuries, pointing out its value in proving the existence of a brain stem lesion. He noted that feelings of uneasiness and difficulty in looking to one side may be present without actual paresis of ocular muscles. Gurevich,[3] in 1938, described what he called the oculostatic syndrome in head injuries and outlined a method of clinical examination which included the effect of conjugate gaze on body position. He observed occasional falling backward with upward gaze, falling forward with downward gaze, and convergence and lateropulsion with lateral gaze. He also noted distress with conjugate gaze while seated. Gurevich assumed the existence of traumatic lesions impairing supranuclear vestibulo-ocular connections without anatomical data to support this hypothesis. Parland,[4] in 1947, in a small series of head injuries, confirmed the observations of Gurevich and corroborated the clinical value of the oculostatic syndrome.

There have been no other detailed studies of discomfort with conjugate gaze. In discussing the value of ocular signs in the diagnosis of the postconcussion syndrome, Beck [5] mentioned disturbances of upward gaze, implying limitation of such

† Dr. Savitsky died Sept. 4, 1953.

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1. Savitsky, N., and Madonick, M. J.: Statistical Control Studies in Neurology: I. The Babinski Sign, Arch. Neurol. & Psychiat. **49**:272 (Feb.) 1943; II. The Pronator Sign of Wilson, A. M. A. Arch. Neurol. & Psychiat. **67**:344 (March) 1952; Madonick, M. J.: Statistical Control Studies in Neurology: III. The Hoffmann Sign, ibid. **68**:109 (July) 1952.

2. Mann, L.: Über ein häufig zu beobachtendes Syndrom bei Commotio bzw. Contusio cerebri, Deutsche med. Wchnschr. **57**:2172 (Dec. 25) 1931.

3. Gurevich, M. O.: The Oculostatic Phenomenon, Nevropat. i psikhiat. **7**:6, 1938.

4. Parland, O.: Oculostatic Syndrome Following Brain Trauma, Nord. med. **34**:1044 (May 2) 1947.

5. Beck, G. M.: Diagnosis of the Postconcussional State, New York J. Med. **46**:2642 (Dec. 1) 1946.

eye movements, rather than discomfort. Janzen,[6] in describing one of his cases of head injury, reported dizziness on looking upward. Lapidari and his collaborators,[7] in their textbook on head injuries, mentioned difficulty with lateral gaze. Calendoli,[8] in his recent outline of neuro-ophthalmology, reported a disturbance of lateral eye movements as a sequel of head injury but gave no clear description of subjective distress during such movements. Köbcke[9] discussed the work of Mann on disturbance of conjugate gaze following head injuries but did not refer to his own experiences. Birkmayer[10] mentioned distress with lateral gaze in two cases of hemianoptic field defects following gunshot wounds to the head.

Gurevich[3] repeatedly referred to the oculostatic syndrome as a sign of cerebral concussion. Beck[5] emphasized the value of ocular signs (disturbance of upward gaze, convergence weakness) in diagnosis of the postconcussion syndrome. Brown,[11] da Rocha Filho,[12] and others refer to vestibular and cochlear disturbances as objective signs of cerebral concussion. Brunner,[13] however, pointed out that loss of excitability of the labyrinths following commotio cerebri indicates more extensive involvement, with probable concussion of the inner ear. These so-called objective signs point to the probable existence of small focal lesions. Carrillo,[14] in 1944, clearly differentiated between the subjective syndrome and the so-called objective signs following commotio cerebri. The objective signs indicate the presence of microcontusions, small lacerations, or circumscribed parenchymatous changes. Distress with conjugate gaze cannot be considered part of the postconcussion syndrome, because it is indicative of a focal traumatic lesion in the vestibulo-ocular connections of the brain stem or other parts of the brain. The mildest pyramidal tract signs or organic sensory changes following head injuries are generally accepted as evidence of focal injury to brain tissue.

Discomfort with conjugate gaze can be considered part of the oculostatic syndrome described by Gurevich.[3] Reactions to pursuit and command conjugate eye movements were studied with the subject in the sitting and standing positions. In a few cases there was a definite difference in the discomfort experienced during

6. Janzen, R.: Klinische Erfahrungen bei Gehirnverletzungen: III. Die Auswertung der initialen Allgemeinensymptome für die Beurteilung intrakranieller Verletzungsfolgen, Deutsche Ztschr. Nervenh. **163**:354, 1950.

7. Lapidari, M.; Mucchai, L., and Porta, V.: Traumi cranici: Chirurgia—neurologia—radiologia, Belluno, Edizioni Casa Editrice Libraria Antonio Salvador, 1938.

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9. Köbcke, H.: Das Schädel-Horn-Trauma: Behandlung, Folgen und Begutachtung, Leipzig, Georg Thieme, 1944.

10. Birkmayer, W.: Hirnverletzungen mechanismus: Spätkomplikationen, Funktionswandel, Vienna, Springer-Verlag, 1951, pp. 260-263.

11. Brown, M. G.: The Post-Concussion Syndrome, New York J. Med. **41**:1065 (May 15) 1941.

12. da Rocha Filho, J. S.: Psicoses traumáticas: (estudo clinico e médico-legal), Bahia, Brazil, Imprensa Ojicial, 1946, p. 46.

13. Brunner, H.: Disturbance of the Function of the Ear After Concussion of the Brain, Laryngoscope **50**:92 (Oct.) 1940.

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these two types of conjugate eye movements, emphasizing once more the existence of a physiologic distinction. Discomfort with conjugate gaze was occasionally noted only with upward, downward, or lateral gaze in one direction. In one case discomfort was noted only during convergence. In a very small percentage of the cases studied, there were marked dizziness and swaying when conjugate eye movements were tested with the subject standing. A tendency to fall to one side with lateral gaze was observed a few times. In most cases the patients complained of dizziness, tenseness in the eyes, and even blurring of vision. Many patients closed their eyes during the tests even while seated, indicating a desire to terminate the examination. On very rare occasions, patients complained of pain in the eyes during ocular movements.

There seems to be some relation between ocular asthenopia or ready blurring of the printed page following head injuries and discomfort with conjugate gaze. Ocular asthenopia was encountered in 2.3% of all cases of head injuries and in 12% of the cases in which there was discomfort with conjugate gaze. Gurevich [3] mentioned the probable impairment of cogwheel jerks of the eyes which are normally present during reading. Further study of eye movements during reading by specialized techniques is advisable after head injuries.[15]

Nerve deafness was found in 10% of the 2,604 cases of head injuries in the present series. Evidence of inner ear involvement (cochlear impairment) was noted in 20% of the injured who complained of discomfort with conjugate gaze. No spontaneous nystagmus was noted in any of the cases. The available facts are against the hypothesis that inner ear injuries can account for the discomfort with conjugate gaze. In 100 cases there was discomfort with conjugate gaze without any evidence of inner ear involvement. It is more likely that the same blow which injures the inner ear is frequently transmitted to the central nervous system.

Discomfort with conjugate gaze was found in 138 (5.3%) of the 2,604 cases of head injuries. In 100 of these cases discomfort with conjugate gaze was the only objective sign. It was not found in children. No particular age group was more severely affected than others. Eighteen of the 138 injured who showed this sign were examined more than one year after the trauma. It was still demonstrable 8 and 12 years after the head injury. Most of the patients were examined during the first six months after the head blow. In all the cases in this series of head injuries an interval of at least three weeks had elapsed before the patient was first examined. There were no hemianoptic field defects in any of the 138 cases. There was no paralysis of conjugate gaze in any of the cases in which distress with ocular movements was present.

Two control groups were studied for discomfort with conjugate gaze. Of 3,500 patients with conditions diagnosed as psychoneuroses, with an almost equal number of males and females, all over 18, only 1 woman, of 27, showed definite discomfort with conjugate gaze in all directions during command and pursuit eye movements. Five of 21,000 draftees showed discomfort with conjugate gaze. Four of these five had sustained definite, verifiable head injuries two to five years previously, and one had a history of two head injuries.

15. Savitsky, N., and Winkelman, N. W.: Cogwheel Phenomenon of the Eyes: Its Clinical Significance, Arch. Neurol. & Psychiat. **57**:362 (March) 1947.

Discomfort with conjugate gaze can be considered a sign of organic injury to the brain. This ocular complaint and finding, which may be the only objective evidence of organic injury to the brain, is probably due to injury to the supranuclear vestibulo-ocular mechanism within the brain stem.

The significantly low incidence of this disturbance of the vestibulo-ocular system in the two control groups corroborates the clinical value of this sign.

CONCLUSION

Discomfort with conjugate gaze was tested in 2,604 patients with head injuries, 3,500 psychoneurotic patients, and 21,000 draftees.

Discomfort with conjugate gaze was present in 138 (5.3%) of the patients with head injuries, in 1 (0.028%) of the psychoneurotic patients, and in 5 (0.024%) of the draftees.

There appears to be some relation between ocular asthenopia and discomfort with conjugate gaze.

No clear relation between discomfort with conjugate gaze and nerve deafness was noted.

THE CILIOSPINAL REFLEX IN INJURIES OF THE CERVICAL SPINAL CORD IN MAN

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IN PURSUING some of the defects of autonomic regulation in injuries of the cervical spinal cord, attention was directed to the pupillodilation reflex elicited by painful stimuli (ciliospinal reflex) (Claude Bernard) to the cheek or neck.

Ranson [1] (1947) states that this pupillary skin reflex can be induced by any strong sensory stimulation. The pathway is by way of fibers of these sensory nerves and their central connections in the brain stem and spinal cord and then by way of the sympathetic outflow from the intermediolateral column to the dilators of the iris.

However, this mode of transmission is now controversial since in the cat this reflex has been shown to be due to inhibition of tonic activity of the Edinger Westphal nucleus and is not impaired in section of the cervical sympathetic trunk. But in the monkey and *probably* in man reflex dilation of the pupil may be evoked by activation of its sympathetic innervation as well as by inhibition of its parasympathetic innervation.

In other words, the pathways of reflex pupillary dilation in man are still a matter of controversy.

We shall show that in lesions of the cervical cord in which stimuli from above cannot reach the sympathetic outflow in the spinal cord pupillary dilation is absent, as observed in the ciliospinal reflex when the face is stimulated. However, when the chest below the level of the lesion is similarly stimulated, pupillary dilation does occur and can be mediated only through known pathways causing sympathetic excitation (Fig. 1).

METHOD

From the group of spinal cord-injured patients at the Veterans Administration Hospital, Hines, Ill., 19 with lesions in the cervical segment were selected for this study. Observations were then made on associated cervical-root damage by reflex and electrical examination, type of sweating response, pilomotor response, size of pupils, size of palpebral fissures, and the ciliospinal reflex. Of the 19 patients utilized in this experiment, 14 had physiologically complete lesions, and 5 physiologically incomplete lesions, of the cervical cord. However, in the latter

Dr. L. J. Pollock helped us in this investigation.

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From the Department of Nervous and Mental Diseases, Northwestern University Medical School, and the Division of Neurology, Veterans Administration Hospital, Hines, Ill.

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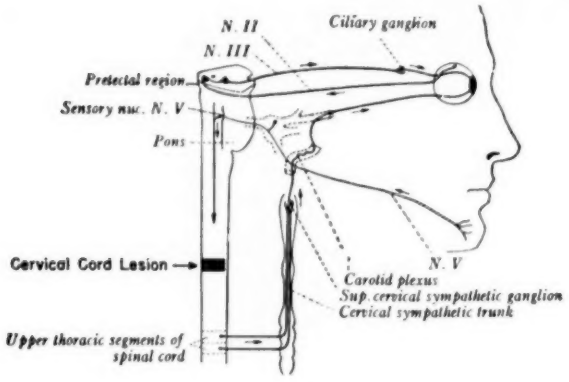

Fig. 1.—Pupillary reflex arcs.

Fig. 2 (A. J. A.).—*A*, resting (control): right pupil 4 mm.; left pupil, 4 mm. *B*, stimulation of chest: right pupil, 4.5 mm.; left pupil, 4.5 mm. *C*, stimulation of right cheek: right pupil, 5.5 mm.; left pupil, 5.5 mm.

there was loss of pain in the midthoracic region and below, which was the segment stimulated with faradic current. The duration of the injury was from five months to one year in 5 patients; from one to two years in 4 patients, and over two to seven years in 10 patients.

CONTROLS

In 16 physicians and technicians, elicitation of the ciliospinal reflex was attempted by means of a pin, constant-current square-wave stimulator, and a faradic coil (1½ volts in the primary). It was most constant with the last. Pin stimulation was too unreliable.

In 11 of 14 normal subjects, a constant-current square-wave stimulator with 3 to 5 ma. gave unilateral 1-mm. dilation of the pupil. In two persons no dilation was observed, and in one the response was questionable.

In seven persons, pupillary dilation was definite, with at least 1 mm. of dilation, and was found easier to elicit using a faradic coil at one-half maximal strength with 1½ volts in the primary. The stimulus was tolerably painful. In four of these seven subjects the lower chest was stimulated with faradic current, but no pupillary dilation was evident. Therefore, normally pupillary dilation occurs well with faradic stimulation of the face and is greatest on the same side as the stimulus. With the same intensity of current, the reflex is not produced, or only slightly elicited, by stimulation on the chest wall (Fig. 2*B*). The skin of the face is the optimal area for this reflex.

The blood pressure was determined before faradic stimulation and during stimulation of the chest and face.

Pupillary Dilation in 19 Patients (38 Sides)

	Present	Absent	Doubtful
Faradic stimulation of chest (unilateral)	34 (90%)	3	1
Faradic stimulation of face	1	27 (71%)	10 (26%)
Psychic stimulation	10 patients	.....	.....

RESULTS

Faradic stimulation on the chest at approximately the sixth thoracic skin segment produced dilation in 17 patients, or 34 of the 38 sides, or in 90% (Table). The dilation was seen best on the side opposite that stimulated in all 17 patients. In three instances (two patients) no reaction was seen, and in one the dilation was doubtful. At all times the reaction was witnessed by one or two other physicians. The range of dilation was 0.5 to 4 mm., with a median of 1 mm.

In one patient (P. G.) there was a proved anatomical separation at the sixth cervical segment of the spinal cord. The pupillary dilation was definite with stimulation of the chest and absent with facial stimulation.

In three instances (two patients) in which no pupillary dilation from stimulation of the chest occurred, there was atrophy of the upper extremities with areflexia in one patient (R. F.), and in the other (J. M.) there was marked atrophy of the small hand muscles with absence of ulnar and triceps reflexes, while the radial and biceps reflexes were active. This is presumptive evidence of possible root lesions in the lower cervical region which would interfere with the efferent path of the ciliospinal reflex. Further electrical evidence of this will be the work of another project in process.

When this experiment was repeated by stimulating the face, no dilation was seen in 27 instances; the dilation was doubtful in 10 instances, and in only 1 instance

did there appear a dilation of one pupil. In this one patient the chest stimulation caused an increase of 2 mm. in the pupil, while with stimulation of the face the increase was only 0.5 mm. This may have been a coincidental psychic increase in pupillary size.

In 10 patients dilation of the pupil was observed without any specific stimulation, but it was felt that during the explanation to the patient and after the procedure

Fig. 3 (T. P.).—*A*, resting: right pupil, 3.5 mm.; left pupil, 3.75 mm. *B*, stimulation of chest: right pupil, 4 mm.; left pupil, 5 mm. *C*, stimulation of right side of face: right pupil, 3.5 mm.; left pupil, 3.5 mm.

was begun there was definite psychic stimulation (diminution of inhibition through the oculomotor nerve to the ciliary muscle).

Photographs (flash) were taken of the ciliospinal or sensory reflex in two patients and in a control (A. J. A.). When the chest was stimulated with the faradic current in the control, only a 0.5-mm. dilation of the pupils occurred (Fig. 2 *B*). When the right side of the face was stimulated, both pupils increased by 1.5 mm. (Fig. 2 *C*). This reaction was prompt, and is the normal response.

In one patient (T. P.), when the right chest was stimulated, the right pupil increased 0.5 mm., to 4 mm., and the left pupil increased 1.5 mm. to 5 mm. (Fig. 3 *B;* Figure 3 *A* shows the resting control). When the face was stimulated, there was no change in the pupil (Fig. 3 *C*).

In the second patient (C. L.) the initial pupillary diameters were 5 mm. (Fig. 4 *A*). Stimulation of the right chest produced an increase of 0.5 mm., to 5.5 mm. on the right and an increase of 0.75 mm., to 5.75 mm. on the left (Fig. 4 *B*). Stimulation of the face produced no increase in pupillary size (Fig. 4 *C*).

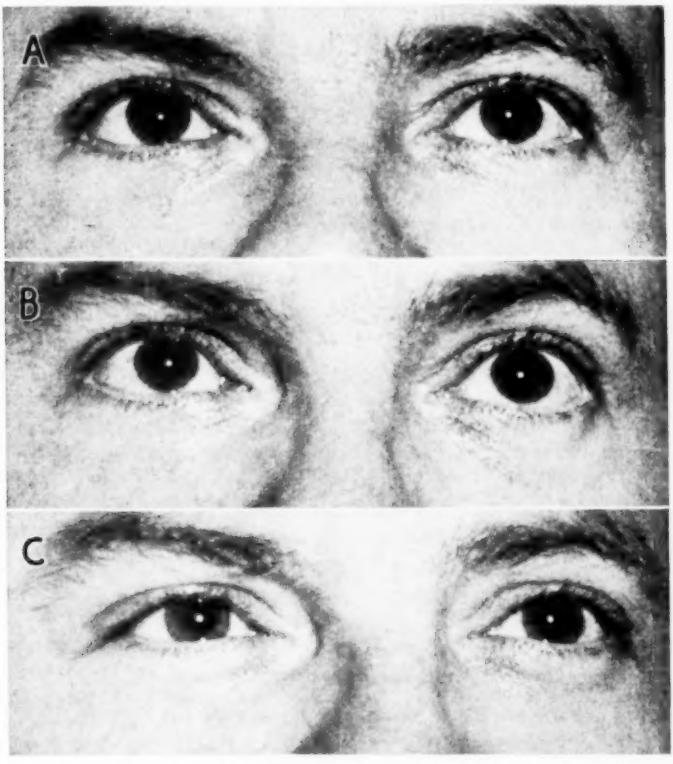

Fig. 4 (C. L.).—*A*, resting: right pupil, 5 mm.; left pupil, 5 mm. *B*, stimulation of right chest: right pupil, 5.5 mm.; left pupil, 5.75 mm. *C*, stimulation of right side of face: right pupil, 5 mm.; left pupil, 5 mm.

ASSOCIATED SYMPATHETIC SIGNS

In 13 patients the blood pressure was taken before and during faradic stimulation. When the chest was stimulated, an increase in blood pressure was recorded, with a range of 2 to 70 mm. Hg systolic and a median increase of 20 mm. Hg. Return to normal blood pressure was slow (lack of inhibitory impulses from supra-segmental centers).

When the face was stimulated, no increase of blood pressure was recorded.

In seven instances there was a pilomotor response, in four above the level of the lesion and in 3 below. In three instances reflex sweating of the face was produced at the time of faradic stimulation. All this occurred only when the chest was stimulated. The elevation of blood pressure, pilomotor response, and sweating in addition to the pupillary dilation, are all indicative of sympathetic excitation.

ANALYSIS OF HORNER'S PHENOMENON

In the 24 patients with cervical cord lesions, observations were made on pupillary size. The range in diameter was 1.5 to 4 mm., with a median of 2 mm. All pupils reacted to light, in accommodation, and consensually. In 11 patients the pupils were slightly unequal. Flash photographs of the pupils in relative darkness revealed larger than-normal pupils. This was observed by Mutch [2] in 1936.

In 10 patients the palpebral fissures were unequal, but in only 4 was there a smaller pupil on the side of the smaller palpebral fissure.

Enophthalmos was not observed, and this probably does not occur with the Horner syndrome in man.

In 13 of these patients there was a decrease to absence of deep reflexes in the seventh to the eighth cervical segment.

REACTION TO DARKNESS

Duke-Elder [3] (1949) refers to the "dilation of the pupil in darkness as not necessarily a reversal of the light reflex. The pathway corresponds initially to that of the light reflex, as far back as the superior colliculus; there the two must part company, and while the constrictor fibers run into the pretectal region, the dilator fibers probably descend within some extrapyramidal (tectospinal?) tract through the midbrain, pons, medulla and cervical cord to reach the ciliospinal center." We attempted to disprove or verify this statement. In six patients with a complete lesion of the cervical spinal cord the pupil in ordinary light ranged from 2 to 4 mm. When the room was darkened, the pupils increased in size from 1 to 2.5 mm., with a median increase of 1.5 mm. This disproves the concept of the darkness reflex as having afferent pathway down to the ciliospinal center and would, rather, be in favor of a reversal of the light or inhibition of the light reflex. This agrees with the statement by Best and Taylor.

COMMENT

Pupillary dilation may be produced by psychic, cortical, and painful somatic stimuli (Kestenbaum and associates [4]). When it is elicited by pinching the face or the skin of the neck, it is called the ciliospinal reflex (Claude Bernard) Spiegel and Sommer,[5] Ranson,[1] Strong and Elwyn.[6]

2. Mutch, J. R.: The Pupil After Cervico-Thoracic Sympathetic Ganglionectomy: Photographic Observation in Man, Edinburgh M. J. **43**:743-746, 1936.

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4. Kestenbaum, A.: Clinical Methods of Neuro-Ophthalmologic Examination, New York, Grune & Stratton, Inc., 1946, p. 299.

5. Spiegel, E. A., and Sommer, I.: Neurology of the Eye, Ear, Nose, and Throat, New York, Grune & Stratton, Inc., 1944, p. 435.

6. Strong, O. S., and Elwyn, A.: Human Neuroanatomy, Baltimore, William Wood & Company, 1943, p. 249.

In a historical review, Kuntz [7] (1945) referred to Budge [8] (1855), who described the emergent fibers from the spinal cord in the upper thoracic segments as the ciliospinal center. As early as 1772 Purfour and Petit were familiar with changes described in section of the cervical trunk. Langendorff [9] (1909) described further the phenomenon we call Horner's syndrome following sympathetic interference.

Ingram, Ranson, and Hannett [10] (1931) have shown that dilation of the pupil may be elicited by stimulation regularly of any point in the tegmentum of the mesencephalon and pons. They inferred that the stimulus probably affected descending visceral fibers widely scattered in the tegmental portions of the brain stem.

With respect to sensory stimuli from the trunk, Bain, Irving, and McSwiney [11] and Harper, McSwiney, and Suffolk [12] (1935) stimulated the vagus and splanchnic nerves in the abdomen and caused pupillodilation. By cutting the cervical cord at the second or third segment, this reflex was retained. They proved that the intactness of the third to the fifth dorsal nerve roots allowed the pupillodilation reflex to be elicited.

Harper and McSwiney [13] (1937) demonstrated that somatic or visceral impulses are transmitted in the lateral funiculus of the spinal cord on the same or the opposite side.

Hutchinson (1878) suggested that pupillary dilation in cerebral trauma was due to impaired function of the oculomotor nerve. Braunstein (1894), cited by Kuntz, tried to explain pupillary dilation by relaxation of the sphincter of the pupil through the third nerve. Sherrington (1900) also postulated this in dogs but gave no proof. Karplus and Kreidl [14] disagreed in 1912, because by cutting the cervical sympathetic fibers they abolished this reaction. In 1918 [15] they changed their conclusions because pupillary dilation by stimulation of the sciatic nerve was abolished when the upper cervical cord was cut.

Ury and Gellhorn [16] (1939), in cats, proved that painful stimulation to the paws or sciatic nerve caused parasympathetic inhibition and pupillary dilation. Harris, Hodes, and Magoun [17] confirmed the parasympathetic inhibition and worked out the afferent pathways for the pupillodilator reflex in the cat. Weinstein and

7. Kuntz, A.: The Autonomic Nervous System, Ed. 3, Philadelphia, Lea & Febiger, 1945, p. 337.

8. Budge, J.: Über die Bewegungen der Iris, Braunschweig, Fr. Vieweg & Son, 1855.

9. Langendorff, O.: Beiträge zur Reflexlehre, Arch. ges. Physiol. **127**:507-528, 1909.

10. Ingram, W. R.; Ranson, S. W., and Hannett, F. J.: Pupillary Dilatation Produced by Direct Stimulation of Tegmentum of Brain Stem, Am. J. Physiol. **98**:687-691, 1931.

11. Bain, W. A.; Irving, J. T., and McSwiney, B. A.: Afferent Fibers from the Abdomen in the Splanchnic Nerve, J. Physiol. **84**:323-333, 1935.

12. Harper, A. A.; McSwiney, B. A., and Suffolk, S. F.: Afferent Fibres from the Abdomen in the Vagus Nerves, J. Physiol. **85**:267-276, 1935.

13. Harper, A. A., and McSwiney, B. A.: Ascending Spinal Pathways of the Pupillodilator Fibers, J. Physiol. **90**:395-402, 1937.

14. Karplus, J. P., and Kreidl, A.: Gehirn und Sympathicus: II. Sympathicusleitung im Gehirn und Halsmark, Arch. ges. Physiol. **143**:109-127, 1912.

15. Karplus, J. P., and Kreidl, A.: Gehirn und Sympathicus: IV., Arch. ges. Physiol **171**:192-200, 1918.

16. Ury, B., and Gellhorn, E.: Role of the Sympathetic System in Reflex Dilation of the Pupil, J. Neurophysiol. **2**:268-275, 1939.

17. Harris, A. J.; Hodes, R., and Magoun, H. W.: The Afferent Path of the Pupillodilator Reflex in the Cat, J. Neurophysiol. **7**:231-244, 1944.

Bender [18] (1941), feeling there might be a genus difference, repeated the work of previous investigators on the cat and then the monkey. Acute experiments were performed to prevent epinephrine sensitivity. In cats, pupillodilation was present after cervical sympathetic or trigeminal nerve section or both. This dilation was prompt but was not accompanied by retraction of the nictitating membrane or widening of the palpebral fissure. When the occulomotor nerve was cut, this reaction was abolished even with an intact cervical sympathetic trunk. Destruction of the caudal portion of the hypothalamus did not interfere with the dilation of the pupil. This confirms previous observations, i. e., those of Harper, McSwiney, and Suffolk [12] (1935) and Ury and Gellhorn [16] (1939) that the reflex was due to parasympathetic inhibition. When the same experiment was repeated in the monkey, mydriasis was produced by mechanical or electrical stimulation of the sciatic nerve. Acute section of the cervical sympathetic trunk eliminated the pupillodilation except for a few cases in which slight dilation was detected. This dilation was not abolished by sectioning the oculomotor nerve. Further work was done on diencephalic, thalamic, and hypothalmic stimulation in the cat. This caused bilateral dilation of the pupil without affecting the nictitating membrane. The reflex was unaffected, or only slightly so, by cervical sympathetic section and was abolished by oculomotor section, again proving that pupillodilation was due to parasympathetic inhibition. In certain areas of the ventral hypothalamus, stimulation produced maximal dilation of the pupil and retraction of the nicitating membrane. This reaction was reduced by section of the cervical sympathetic trunk, but after oculomotor section additional dilation occurred, indicating sympathetic activity. Repetition of these experiments in the monkey revealed that the dilation from hypothalamic stimulaton was abolished by section of the cervical sympathetic trunk but was not abolished by sectioning the third cranial nerve. This is indicative of sympathetic stimulation in the monkey.

Weinstein and Bender conclude that reflex pupillodilation is due both to parasympathetic inhibition and to sympathetic stimulation but that in the monkey the latter mechanism prevails.

There is general agreement (Best and Taylor,[19] 1950) that the afferent pathways of the ciliospinal reflex are the pupilloconstrictor fibers in the lateral funiculus and in the brain stem as far as the lateral geniculate body. That the pathways is in the lateral funiculus agrees with our results in that stimulation of the chest produced the greatest pupillary dilation on the opposite side. Furthermore, in those patients with physiologically incomplete lesions, touch was intact or recovered but there was analgesia. From here the pathways are not clear, but they descend through the tegmentum of the midbrain, the reticular formation of the pons, and the medulla and spinal cord to the ciliospinal center.

Foerster [20] (1936), in discussion of human clinical material, i. e., spinal cord injuries, stated that any disturbance above the first dorsal nerve root produces pupillary dysfunction and that with interruption from the diencephalon there are miosis and enophthalmos. We were unable to confirm this finding since no clear-cut Horner syndrome was present with lesions solely of the spinal cord. He further

18. Weinstein, E. A., and Bender, M. B.: Pupillodilator Reactions to Sciatic and Diencephalic Stimulation: A Comparative Study in the Cat and Monkey, J. Neurophysiol. **4**:44-50, 1941.

19. Best, C. H., and Taylor, N. B.: The Physiological Basis of Medical Practice, Ed. 5, Baltimore, Williams & Wilkins Company, 1950.

20. Bumke, O., and Foerster, O.: Handbuch der Neurology, Berlin, Springer-Verlag, 1936, Vol. 5, pp. 227-228.

observed that after acute interruption of the cervical spinal cord the pupillary reaction is abolished and slowly returns. The pupillary reflexes are irritable, and slight stimuli from below can produce dilation of the pupil. In addition, in complete lesions above the first thoracic segment, the pupils may react to stimulation of the face and neck, proving that sensory stimulation may be parasympathetic.

Foerster also emphasized that irritability of the pupil causes a changing pupil, called by Marie [21] a *miosis à bascule* (teeter-totter; fluctuating). Pupillodilation on severe pain after sympathetic interruption is slight and inconstant. It should be remembered that Foerster's observations were on cases of relatively acute spinal cord injuries.

As shown by Pollock and associates [22] (1951) in spinal cord injuries specifically in the cervical cord, there is an interruption of descending suprasegmental impulses to the sympathetic outflow, which produces defects in regulation of such functions as sweating, heat production, and blood pressure. Furthermore, as with reflex activity, interruption of inhibition impulses from above resulted in excessive reflex sympathetic function.

There is, then, evidence pro and con for pupillary dilation as sympathetic excitation and/or parasympathetic inhibition in animals. In our experiments, after the cervical cord is interrupted (Fig. 1), any painful sensory stimuli are prevented from ascending to the hypothalamus and cortical centers, and likewise inhibitory impulses from suprasegmental centers are prevented from descending through the cervical spinal cord. Therefore, any painful stimulus below the lesion causing pupillary dilation must be due to sympathetic excitation.

SUMMARY AND CONCLUSIONS

Although there is evidence in the literature that pupillary dilation is by way of parasympathetic inhibition and sympathetic excitation, the results of our work can lead only to the one conclusion that in man it is wholly sympathetic.

Inasmuch as a lesion of the cervical spinal cord precludes stimuli below the level of the lesion from ascending to the brain stem, or inhibitory fibers from suprasegmental levels from descending, any reaction from below must be by way of the sympathetic outflow by known pathways. Painful stimulation of the chest travels up the spinal cord and passes out by the sympathetic outflow to dilate the pupil, as well as give other symptoms of increased sympathetic function. Also, painful stimuli above the lesion, i. e., of the face, in an attempt to cause a ciliospinal reflex are blocked. They make central connections and may go down the brain stem, but are prevented from synapsing with the intermediolateral cells in the spinal cord. Thus no pupillary dilation is seen. This stimulation of the face, however, does not prevent inhibition through the parasympathetic, but since no pupillary dilation occurred in man, this is not the mode for pupillary dilation for painful stimuli.

In lesions of the cervical spinal cord in man the Horner syndrome is not produced.

The dilation of the pupil to darkness is not due to sympathetic stimulation by way of the ciliospinal center but is most likely a reversal of the light reaction.

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21. Marie, P.: Marie's Bénisty, Rev. neurol., 1915.

22. Pollock, L. J.; Boshes, B.; Chor, H.; Finkelman, I.; Arieff, A. J., and Brown, M.: Defects in Regulatory Mechanisms of Antonomic Functions in Injuries to the Spinal Cord, J Neurophysiol. **14**:85-93, 1951.

HALLUCINATIONS IN BRAILLE

Effects of Amygdaloidectomy

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VISUAL hallucinations are uncommon in the blind, usually consisting of patterns or moving shapes, either in shades of gray or in colors, and variously described as terrifying or amusing. Words and letters are apparently very rare, and we have found no reference to hallucinations in shorthand or other symbols. Hence, a report on a patient who experienced hallucinations in braille code seems worth while. Their disappearance after amygdaloidectomy may throw light upon the function of this poorly understood body and upon the mechanism of hallucinations.

REPORT OF A CASE

B. H. was first seen in 1934, at the age of 13 years, with headache, vomiting, choked disks, and staggering, due to cerebellar tumor. A cystic astrocytoma was removed by Dr. H. H. Schoenfeld, with rapid recovery except for residual blindness. The girl went to a school for the blind and became so expert in braille that for a number of years she was able to support herself in the Braille Division of the Library of Congress. She was later employed in the Institute for the Blind in Washington, and during the war worked in a defense plant. She was a serious, rather engaging young woman who was seen from time to time in connection with her studies and who, except for the blindness, was considered normal. Vision was 8/200 in the right eye, with some light perception in the temporal field of the left eye.

A change was noted in the patient's personality in 1950, when she became seclusive and resigned from her position. Her sister reported that the girl often talked to herself in an angry, argumentative manner. When she came under observation again in January, 1952, it was because of marked schizoid dissociation with visual and auditory hallucinations. Aside from these disturbing experiences, there was little abnormality. The patient was correctly oriented; her memory was excellent, and her affect was lively. There was no history of seizures or of clouded states. The electroencephalogram was normal. Aside from secondary optic nerve atrophy and wide-searching movements of the eyes, not true nystagmus, the neurological examination revealed only slight intention tremor of the upper limbs and mild instability in walking. The Romberg sign was negative. She was very articulate and, probably because of her long acquaintance, yielded more of her secrets than might have been expected.

The following paragraphs were abstracted from a tape record of interviews before amygdaloidectomy on the right side: The patient was first placed by herself in a soundproof room for a period of 25 minutes. During this time no articulate speech was recorded, even with a supersensitive microphone. The patient was then asked about her experiences during this period:

"F.: Tell me what was coming through.

"B.: At the same moment you came in?

"F.: Yes, what was coming through?

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"B.: The very second you came in the word 'defense plant' came in my mind.

"F.: Did that come as an actual thing you could hear?

"B.: No, sir.

"F.: Just an idea?

"B.: You know, it seems to come from within my head and the lettering in braille lettering. It doesn't come out in handwriting or print. It seems to come out in braille lettering, like in front of my forehead, in front of my eyes. I see the words 'defense plant' as I think of it.

"F.: That's an amusing thing.

"B.: It really is. It's in letters, but it's in braille. It has been like that since I have been home at various times, you know. It comes out in braille code.

"F.: Were your eyes open at that time?

"B.: Yes; they've been open the entire time. What I actually thought in my mind would sort of flow out of my mind and seem to focus in front of it. And it comes out in braille writing. At the same time I think of it—both together.

"F.: That's probably the first time we've had an actual recording of the experience coming out in braille.

"B.: Is that right?

"F.: Where did it come from? Do you have any idea where it came from?

"B.: Why, from my own thoughts. Because I did work in a defense factory; so I just happened to think of the defense factory the second you walked in the door, and it came out at the time I thought of it and it appeared before my eyes, sort of. I don't see the defense factory, but just the word, the two words, I mean."

Pneumoencephalography was performed on Feb. 25, but the ventricles failed to fill. After this procedure the left arm and leg were partly paralyzed. Two days later amygdaloidectomy was performed on the right side, with the use of local anesthesia. No tape record was taken because the patient was too preoccupied and distressed by the operation.

The technique of amygdaloidectomy was briefly as follows:

A 3-cm. trephine opening was made low in the temporal region on the right side. The dura was opened, and the middle temporal convolution was slit horizontally. Dissection of the white matter was carried to a depth of 3 or 4 cm., when the instrument entered the temporal horn of the ventricle. Gentle retraction permitted recognition of the serrations of the pes hippocampi. Because of the dilated ventricles, it was particularly easy to expose the amygdaloid nucleus, in the anteromedial wall of the tip of the ventricle. A small piece of this bulging gray eminence was removed for histologic identification and the rest of the nucleus ablated by suction.

After amygdaloidectomy, the patient was again interviewed with the aid of a tape recorder. She was euphoric, talkative, and self-confident. There was a distinct change in her speech. While there was some tendency to slur certain words, the greatest change was in the pitch and timbre. Each syllable emphasized would reach a rather high pitch; and since the emphasis was frequent, the voice was very uneven. This unevenness was noted even more in singing. The patient had sung a good deal in earlier years, and her voice, although not trained, was a high soprano. For a few days after operation, she was often heard singing or humming to herself. When she sang upon request, the result was like that of a child of 6 years, very uneven in pitch and emphasis, with a tendency to run through the pauses and to hurry the phrases. Speech and singing cleared rapidly in the days before her discharge from the hospital.

Three days after amygdaloidectomy, the patient was asked about her hallucinatory experiences.

"F.: Do you think there's been any change in you since the second operation, the amygdaloidectomy?

"F.: No, sir, I don't think so; but, as I said previous to our interview, as far as nervous disposition was concerned, as far as mirror of thought is concerned, that has been improved 100%.

"F.: Tell me more about that. What was that like?

"B.: I remember quite well. If I thought of something in my mind, at a moment's notice, it seemed to flash right in front of my eyes the same very second; so both came together—in my mind and right before my mind in braille code. It wouldn't come out in ink print.

"F.: All right. How about derogatory words?

"B.: Like that word 'louse' I spoke of? No. That word never came out in my memory.

"F.: How about the other ones—bitch, whore?

"B.: No. None of those words ever stuck with me, for the simple reason I would hear them but I would never believe them. It was unbeliev-inconceivable. To me.

"F.: How about that first terrible thing: 'There's the blind bitch'?

"B.: Yes. Well, you see, that took me off guard, unaware; and I couldn't apprehend it—or comprehend it, rather, about my own self. Because I didn't feel it of myself. So I shut the door and went in the house real quickly. It didn't come out in my memory just then and there, but perhaps several weeks later it would reappear. It would be my own voice that would say it again in my head, but the incident would be the same incident of that car parking across the street and someone getting out and saying that as soon as I opened the front door.

"F.: Would you repeat those words?

"B.: That's all he said. Sometimes it's the words, and sometimes it's in braille: 'There's the blind bitch.'"

In the year that followed operation, the patient progressed favorably, regaining fair control of her left hand. She was freed of the hallucinatory experiences. The family reported that her behavior at home was improved and they thought that she might well return to her employment

COMMENT

Louis Braille died in 1852. He was one of the select group of scientists whose contribution is now generally recorded in lower-case letters, like volt and watt and curie. The use of the finger tips to identify configurations of raised dots to convey meaning has been accepted as a means of education for those hampered by poor vision. It may come as a surprise to some that the impressions conveyed are interpreted visually rather than kinesthetically, but casual inquiry among teachers of braille show that the configuration is visualized "in the mind's eye," and that the keyboard of the braille typewriter is memorized according to the visual configuration of the keyboard, after first being established by sense of touch. In order to hallucinate in braille, familiarity with the code is a first essential. Another essential is a dissociation accompanied by a vivid emotional response and projection of the image into the field of vision in front of the eyes. It is likely that extremely defective vision is a third essential, so that subjective phantasms take the place of external objects. Targowla and Picard,[1] in presenting a patient with detachment of the retina in whom visual hallucinations developed in the course of a paranoid psychosis, state: "It is a case of two coexisting affections whose manifestations juxtapose and intertwine, but can still be dissociated so as to live apart. . . . These are not simple delusional ideas evolved by a logical procedure of pure intellect." The patient in their case saw the printed names of various friends of her dead son. She also saw a tomb with two crosses, for her son and for her husband, and was particularly alarmed by a vision of a big brute of a man beating a bat. Weill[2] notes the rarity

1. Targowla, R., and Picard, J.: Hallucinations visuelles élémentaires et conscientes dans un cas de décollement rétinien; intégration sécondaire dans un système délirant; le syndrome du décollement rétinien, Ann. méd. psychol. **86** (pt. 1):136-142, 1948.

2. Weill, G.: Hallucinations visuelles chez les aveugles, Rev. oto-neuro-opht. **17**:294-295, 1939.

of visual hallucinations in the blind, saying also that such hallucinations may first make the patient realize that he is blind. The hallucinations in his case consisted of standing on the border of a lake whose waters were in constant movement and of different colors. Sal y Rosas [3] says that his patient saw objects and animals in lively movement.

Visual hallucinations in the blind are apt to occur long after the development of blindness, sometimes 17 years later, as in the case of Trillot and Carlet-Soulages.[4] One of us recalls a demonstration by Spiller of a blind tabetic man who experienced crises of visual hallucinations along with gastric crises and lancinating pains in the legs. This patient became almost ecstatic in describing the beautiful gardens filled with flowers that he saw during these "optic crises."

Visual hallucinations of complex type have often been described in connection with lesions of the temporal lobe in the remote past by Gowers,[5] and more particularly by Penfield and Rasmussen.[6] Lhermitte [7] has described so-called peduncular hallucinations. Morel [8] says of these: "Nothing is known about the mechanisms or laws of propagation or distribution of these plurisensory stimuli."

The surgical attack upon hallucinations goes back to Burckhardt,[9] who presented his study at the same session of the International Congress of Medicine in Berlin, in 1890, as that at which Horsley [10] reported his studies on excision of the motor convolutions in the treatment of athetosis. Burckhardt thought that the behavior of certain violent schizophrenic patients depended upon auditory hallucinations. Following a suggestion by Mairet,[11] who had described hypertrophied temporal lobes in the hallucinated patient, Burckhardt resected portions of the temporal lobe. The results were encouraging, but the presentation evoked no discussion and lay dormant for nearly 50 years.

Our interest in the temporal lobe was aroused by the fact that prefrontal leucotomy was less successful in hallucinated subjects than in those not presenting hallucinations. We argued, therefore, that the mechanism for the production of hallucinations lay outside the frontal lobe, presumably in the temporal lobe. The uncinate fasciculus connecting the two lobes was found on dissection to pass in the capsule of the amygdaloid nucleus, although no definite implantation could be

3. Sal y Rosas, F.: Fantopsias en un caso de ceguera por infección tuberculosa de los ojos, Rev. méd. peruana **12**:59-66, 1940.

4. Trillot, J., and Carlet-Soulages: Hallucinations visuelles différenciées survenues tardivement chez une femme atteinte de cécité depuis plus de vingt ans, Ann. méd.-psychol. **95** (pt. 2): 109-114, 1937.

5. Gowers, W. R.: The Bowman Lecture on Subjective Visual Sensations, Lancet **1**:1564, 1625, 1895.

6. Penfield, W., and Rasmussen, T.: The Cerebral Cortex of Man: A Clinical Study of Localization of Function, New York, The Macmillan Company, 1950.

7. Lhermitte, J., and de Ajuriaguerra, J.: Hallucinations visuelles et lésions de l'appareil visuel, Ann. méd.-psychol. **94** (pt. 1):321-351, 1936.

8. Morel, F.: Introduction à la psychiâtrie neurologique, Paris, Masson & Cie, 1947.

9. Burckhardt, G.: Über Rindenexcisionen als Beitrag zur Behandlung der Psychosen, Transactions of the Tenth International Medical Congress, Berlin, Vol. 4, 1890, p. 9.

10. Horsley, V.: On the Surgery of the Central Nervous System, Transactions of the Tenth International Medical Congress, Berlin, Vol. 4, 1890, p. 9.

11. Mairet, A.: De la démence mélancholique: Contribution à l'étude de la périencéphalite chronique localisée, et à l'étude des localisations cérébrales d'ordre psychique, Paris, Masson & Cie, 1883.

observed. A survey of the comparative anatomy of the amygdaloid nucleus showed it to be of exceptional size in Chiroptera and Cetacea, who apparently rely upon auditory, rather than visual, mechanisms for orientation. Since cetaceans possess no olfactory apparatus, it seemed logical that the amygdaloid nucleus was largely concerned with the production of sounds that could be identified by the animal upon receiving the echo. We [12] published our observations under the title "Human Sonar," reporting some success with amygdaloidectomy in relieving hallucinated patients of their abnormal phenomena.

In brief, we believe that the amygdaloid nucleus is a mechanism for transforming thought processes into temporally patterned "motor" movements, either of the vocal musculature, as in subjective auditory experiences, or of the still vaguer projections or representations that are experienced through vision, smell, taste, or touch. The emphasis is upon the motor component of hallucinations rather than upon the sensory component.

SUMMARY AND CONCLUSIONS

The case is reported of a young woman who, many years after the onset of blindness, had a schizophrenic reaction with hallucinations of hearing and of seeing. The visions were predominantly in braille. The hallucinations disappeared immediately after unilateral amygdaloidectomy. Suggestions are made as to the motor component of hallucinations and their similarity to the sonar mechanism employed by Cetacea and Chiroptera for the purpose of orientation.

12. Freeman, W., and Williams, J. M.: Human Sonar: Relationship of the Amygdaloid Nucleus to Auditory Hallucinations, J. Nerv. & Ment. Dis. **116**:456-462, 1952.

EFFECT OF CARBON TETRACHLORIDE ON THE NERVOUS SYSTEM

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CARBON tetrachloride, a cheap, noninflammable, effective solvent, has been found to be of increasing usefulness in a variety of industrial operations, including processing of rubber, manufacture of paint, cleaning of fabrics, and degreasing of metal parts. In addition, it is widely used in the home as a cleansing agent. Many instances of poisoning by carbon tetrachloride have been reported, both from industrial and from domestic use, and 55 fatal cases were recorded in this country in 1951. No figures on morbidity are available. Apparently, many cases, particularly of non-industrial origin, are undiagnosed,[1] and there appears to be an increasing ratio of cases of poisoning occurring in the home. This is due largely to a systematic program of safeguards initiated by industry, plant, and state authorities. The domestic consumer, however, is often unaware of the lethal nature of carbon tetrachloride, and the label on the container gives little or no warning but, rather, emphasizes the safety of the product because of its noninflammable character.

Despite the frequency and importance of effects on the central nervous system, there has been no systematic study of the neurological consequences of carbon tetrachloride intoxication. The voluminous literature on the pathophysiology of carbon tetrachloride deals almost exclusively with damage to the kidney and liver, with many meticulous histological studies on most of the organs except the brain. Clinical neurological accounts often are meager, incomplete, and secondary to the pathology in other parts of the body.

NEUROLOGICAL SYMPTOMS

In the last five years, we have encountered 15 cases of carbon tetrachloride poisoning from Gallinger Municipal Hospital; Veterans Administration Hospital, Washington, D. C. (Mount Alto Veterans Hospital), and Georgetown University Hospital. Neurological involvement was present in seven cases.

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Presented at the Seventy-Eighth Annual Meeting of the American Neurological Association, June 16, 1953.

1. (*a*) Farrier, R. M., and Smith, R. H.: Carbon Tetrachloride Nephrosis: Frequently Undiagnosed Cause of Death, J. A. M. A. **143**:965, 1950. (*b*) Myatt, A. V., and Salmons, J. A.: Carbon Tetrachloride Poisoning, A. M. A. Arch. Indust. Hyg. **6**:74, 1952. (*c*) Norwood, W. D.; Fuqua, R. A., and Scudder, B. C.: Carbon Tetrachloride Poisoning: More Regulation, More Education Needed, ibid. **1**:90, 1950.

Of our 15 cases, 13 occurred in the home and 2 in commercial cleaning plants. Of the 13 patients whose poisoning occurred at home, 2 were children who drank the fluid; 2 were adults who accidentally drank carbon tetrachloride, and the rest were exposed by inhalation. Five died. Eleven of the 13 adults were alcoholic, and 4 of the deaths occurred in alcoholics. For the fifth patient who died no history was available. Except for three patients, the poisoning was known to be due to a single exposure.

The neurological signs and symptoms appeared early, often dominated the clinical picture, and, in most instances, consisted of headache, vertigo, weakness, blurring of vision, lethargy, and coma. Tremor and paresthesias were often associated phenomena. Confusion, disorientation, and impaired intellectual faculties were manifestations that appeared later. When this symptom complex is present, the diagnosis is established if the history of exposure to carbon tetrachloride can be obtained. But since alcoholism so often accompanies severe carbon tetrachloride poisoning, and since the patient is often in coma when examined, the neurologist is confronted with the all-too-frequent and vexatious problem of an unconscious patient with evidence of or history of alcoholism. The diagnosis of acute alcoholic intoxication with or without head injury is often incorrectly made. Head injury may be further suggested by the very frequent and typical occurrence of conjunctival hemorrhages in carbon tetrachloride poisoning. Gastrointestinal symptoms, particularly abdominal pain and vomiting, often of bloody material, accompany the acute episode.

The following case typifies the usual clinical concatenation of carbon tetrachloride intoxication.

Case 1.—A man aged 32 was exposed to carbon tetrachloride fumes while cleaning the seats of a car. He was a periodic drinker and had been on a spree the day before. He noted no discomfort while using the fluid but a few hours later had onset of sudden pain in his ribs, which radiated down both legs to his feet and persisted for the next three days. In spite of the pain, the patient lapsed into coma for several hours and awakened to vomit. The next day he passed blood in the urine and in the stools. He had headache and intense weakness. The physical findings were normal except for a slight icteric tinge to the sclerae. The liver was not palpable The neurological and ophthalmologic examinations were noncontributory. Liver function tests were normal. A liver biopsy showed central lobular necrosis consistent with a diagnosis of carbon tetrachloride poisoning. He was discharged from Gallinger Municipal Hospital as recovered six days after admission.

This case demonstrates the usual sequential pattern of clinical phenomena characteristic of carbon tetrachloride poisoning—the fairly abrupt onset of radicular or peripheral neuritis, followed by coma and severe gastrointestinal symptoms, with hemorrhagic diathesis, the last being represented by the hematuria and melena. A history of exposure is the most important single datum and should be sought whenever these symptoms occur. Exposure may take place under various conditions, but in a domestic situation it is usually by inhalation.

Another case of poisoning was that of a garage mechanic who washed automobile parts in carbon tetrachloride. Another patient washed his linoleum floor with carbon tetrachloride. Three patients cleaned upholstered furniture with it. Four cases of poisoning were due to accidental ingestion; e. g., one patient, while drunk, went to the bathroom to urinate. He placed his can of beer on the shelf next to a container of carbon tetrachloride, then picked up the latter and drank it.

Chandler [2] describes carbon tetrachloride poisoning in a 4-year-old child who was exposed to carbon tetrachloride when adhesive tape was removed from her back with the fluid. Hardin [3] reports a similar case in a woman aged 52 who, four hours after drinking 3 oz. (90 cc.) of whisky, removed adhesive tape from her chest with carbon tetrachloride in an unventilated bathroom.

As noted, the preponderance of our patients were alcoholic and, moreover, were drinking alcoholic beverages immediately before, during, or soon after the exposure to carbon tetrachloride. This sinister synergy between alcohol and carbon tetrachloride has been reported frequently,[4] but no satisfactory explanation has yet been found. The simultaneous administration of alcohol to animals greatly increases the toxicity of carbon tetrachloride. Alcohol may increase the rate and degree of absorption [5] in the gastrointestinal tract, but reinforcement of toxic effects occurs in animals and humans even when the carbon tetrachloride is inhaled.[6]

Preexisting alcoholic cirrhosis in humans may play a role, but this factor does not operate in controlled animal experiments. The well-known increased vulnerability of alcoholics to all forms of injury, accidental or intentional, raises the question whether the coexistence of alcohol ingestion and exposure to carbon tetrachloride might not be due to chance. However, in 465, or 37%, of 1,258 autopsy cases of violent deaths reported by Wilentz,[7] the cause was acute alcoholism. In 227 cases the alcoholism was associated with poisoning by various other agents, including chloroform, cyanide, carbon monoxide, and barbiturates. In none was it associated with carbon tetrachloride poisoning.

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2. Chandler, F. A.: The Use of Carbon Tetrachloride in Removal of Adhesive Tape: Report of a Near Fatal Case, J. A. M. A. **107**:2121, 1936.

3. Hardin, B. L.: Poisoning from Carbon Tetrachloride Used in Removing Adhesive Tape from the Skin, M. Ann. District of Columbia **22**:224, 1953.

4. (*a*) Allison, B. R.: Treatment of Acute Carbon Tetrachloride Poisoning: 2 Cases, Ann. Int. Med. **16**:81, 1942. (*b*) Foxell, A. W. H.: Three Cases of Carbon Tetrachloride Poisoning with One Fatality, Brit. M. J. **1**:397, 1951. (*c*) Geraghty, F. J., and Rogers, W. A.: Carbon Tetrachloride Poisoning with Report of Case, West Virginia M. J. **43**:242, 1947. (*d*) Gray, I.: Carbon Tetrachloride Poisoning: Report of 7 Cases with 2 Deaths, New York J. Med. **47**:2311, 1947. (*e*) Hagen, W. S.; Alexander, H. A., and Peppard, T. A.: Toxic Effects of Carbon Tetrachloride: Report of a Case, Minnesota Med. **23**:715, 1940. (*f*) Harris, F. H.: Acute Carbon Tetrachloride Poisoning, U. S. Armed Forces M. J. **3**:1023, 1952. (*g*) Lamson, P. S., and Wing, R.: Early Cirrhosis of Liver Produced in Dogs by Carbon Tetrachloride, J. Pharmacol. & Exper. Therap. **29**:191, 1926. (*h*) McGill, C. M.: Death and Illness from Use of Carbon Tetrachloride, Northwest. Med. **45**:169, 1946. (*i*) Moon, H. D.: Pathology of Fatal Carbon Tetrachloride Poisoning with Special Reference to the Histogenesis of the Hepatic and Renal Lesions, Am. J. Path. **26**:1041, 1950. (*j*) Case 34221, Massachusetts General Hospital, New England J. Med. **238**:776, 1948. (*k*) Perry, W. J.: Carbon Tetrachloride Poisoning: Report of 88 Cases, Army M. Bull. 64, p. 70, 1942. (*l*) Smyth, H. F.; Smyth, H. F., Jr., and Carpenter, C. P.: The Chronic Toxicity of Carbon Tetrachloride: Animal Exposures and Field Studies, J. Ind. Hyg. & Toxicol. **18**:277, 1936. (*m*) Strouse, C. D.: Carbon Tetrachloride Intoxication, California Med. **74**:269, 1951. (*n*) Watts, R. W. E.: Carbon Tetrachloride Poisoning, Lancet **1**:66, 1950. (*o*) von Oettingen, W. F.: Halogenated Hydrocarbons: Their Toxicity and Potential Dangers, J. Indust. Hyg. & Toxicol. **19**:349, 1937.

5. Robbins, B. H.: Absorption, Distribution and Excretion of Carbon Tetrachloride in Dogs Under Various Conditions, J. Pharmacol. & Exper. Therap. **37**:203, 1929.

6. Geraghty and Rogers.[4c] Lamson and Wing.[4g]

7. Wilentz, W. C.: The Alcohol Factor in Violent Deaths, Am. Pract. & Digest Treat. **4**:21, 1953.

Further validation of the specific effect of acute alcoholism in enhancing the toxicity of carbon tetrachloride is demonstrated by several reported instances of mass poisoning with carbon tetrachloride.[8] For example, Harris[4f] reports the exposure of 78 Navy men who cleaned their guns in a large, poorly ventilated room with carbon tetrachloride the day after Christmas. Many were suffering from hang-overs. Of those men with symptoms of carbon tetrachloride poisoning, 63% had ingested alcoholic beverages the night before, or even more recently. Fifteen men showed signs of severe poisoning. All but one had drunk alcoholic beverages. Six of the 15 had to be hospitalized. All six were known to be "steady drinkers," and all had drunk large quantities of some type of alcoholic beverage on Christmas.

MECHANISM OF DAMAGE TO NERVOUS SYSTEM

The mechanism of central nervous system involvement in carbon tetrachloride poisoning has not been elaborated, but from our experience and the cases reported in the literature, it appears that the nervous system may be affected by carbon tetrachloride through three possible mechanisms.

I. Direct toxic effect
   (*a*) Narcosis
   (*b*) Encephalomyelitis
   (*c*) Cerebellar degeneration
   (*d*) Neuritis
      (1) Peripheral
      (2) Optic
II. Hemorrhage
III. Cerebral Fat Embolism

Direct Toxic Effect.—Narcosis: The most important toxic effect on the central nervous system is narcosis. Carbon tetrachloride is similar to chloroform in this respect; in fact, carbon tetrachloride was introduced as an anesthetic in 1847, soon after chloroform was employed, but it was found too toxic. It produces marked respiratory depression and fall in blood pressure, probably due to medullary depression.[9] Addiction to carbon tetrachloride has been described.[10] The following case is illustrative of carbon tetrachloride narcosis.

CASE 2.—A 9-month-old infant, according to his mother, drank 1 oz. (30 cc.) of Carbona. He was admitted to Gallinger Municipal Hospital on Aug. 29, 1949. The stomach was lavaged within one-half hour, but the patient promptly lapsed into stupor for the next several hours and remained lethargic for the next day. He recovered completely and was discharged, without sequela, on the 12th hospital day.

In a similar case[4b] reported in 1951, a 3-year-old girl drank less than a thimbleful of carbon tetrachloride. She became drowsy at once, "but her parents were not

8. (*a*) McGill.[4b] (*b*) Perry.[4k] (*c*) Abbott, G. A., and Miller, M. J.: Carbon Tetrachloride Poisoning: Report on 10 Cases at U. S. Marine Hospital, Seattle, Washington, Since 1937, Pub. Health Rep. **63**:1619, 1948. (*d*) Alha, A.: Carbon Tetrachloride Mass Poisoning, Ann. med. int. Fenniae (Supp. 8) **39**:1, 1950. (*e*) Kugel, V. H.: Acute Toxic Nephrosis in Carbon Tetrachloride Poisoning, J. Mt. Sinai Hosp. **12**:440, 1945.

9. von Oettingen, W. F.: Poisoning: A Guide to Clinical Diagnosis, London, William Heinemann, Ltd., 1952.

10. Hamilton, A., and Hardy, H. L.: Industrial Toxicology, Ed. 2, New York, Paul B. Hoeber, Inc., 1949.

worried by this as it was near her bedtime. Indeed, she was given some fish and chips which had an immediate and most fortunate emetic effect. Her drowsiness increased, however, and she lost consciousness within three-quarter of an hour after taking the poison." Her stomach was lavaged soon after, but she remained unconscious for five and one-half hours.

Allison [4a] records the case of a 9-year-old boy who, while cleaning a book with carbon tetrachloride, found that he liked the odor or the effect of the fluid. He poured it on a blanket, replaced the container, crawled into bed, and covered himself with the blanket. He said he saw stars and then he could not remember anything. A few moments later he was found unconscious. The physician, upon arrival, found the child unconscious and perspiring with flushed face, rapid and thready pulse, dilated pupils, and absence of all deep and superficial reflexes. No clue could be found to what had happened to him, and since sugar was found in the urine, insulin was administered. After several hours, the coma resolved, and the patient was well. Strouse [4m] and Watts [4n] record other instances of narcosis following ingestion of carbon tetrachloride.

A similar narcotic effect can be reproduced in animals.[11] Adams [12] noted a marked depressant action on the central nervous system in rats, manifested by drowsiness or stupor and, with increasing concentration of the poison, loss of equilibrium and coordination and, finally, unconsciousness, terminating in death. In animals that survive the acute depressant action, an additional injury of considerable magnitude was indicated by abnormal behavior and appearance.

Encephalomyelitis: In addition to the characteristic somnolence, lethargy, and coma that the narcotic action of carbon tetrachloride produces, other signs of impaired or disturbed mentation can be produced.[13] Easton [13f] reports a patient who suffered paresthesias of the extremities and unconsciousness, followed by euphoria. Lehman and Flury [13j] produced in experimental human subjects giddiness, restlessness, and euphoria at various controlled concentrations of carbon tetrachloride. McBurney, cited by Hamilton and Hardy,[10] had a patient whose mental symptoms progressed to chronic mania, requiring seven months of institutionalization, after carbon tetrachloride poisoning.

11. von Oettingen, W. F.; Powell, C. C.; Sharpless, N. E.; Alford, W. C., and Pecora, L. J.: Relation Between the Toxic Action of Chloronated Methanes and Their Chemical and Physicochemical Properties, Nat. Inst. Health Bull. 191, Federal Security Agency, Public Health Service, 1949.

12. Adams, E. M.; Spencer, H. C.; Rowe, V. K.; McCollister, D. D., and Irish, D. D.: Vapor Toxicity of Carbon Tetrachloride Determined by Experiments on Laboratory Animals, A. M. A. Arch. Indust. Hyg. **6**:50, 1952.

13. (*a*) Allison.[4a] (*b*) Hamilton and Hardy.[10] (*c*) Ackerman, G., and Ruppert, V.: Symptomatology of Carbon Tetrachloride Poisoning, Deutsches Arch. klin. Med. **189**:458, 1942. (*d*) De, A. C.: Jaundice and Acute Mania Following Combined Carbon Tetrachloride and Oil of Chenopodium Treatment for Hookworm, Indian M. Gaz. **68**:150, 1953. (*e*) Dillenberg, S. M., and Thompson, C. M.: Carbon Tetrachloride Poisoning: Report of 20 Cases with One Death, Mil. Surgeon **97**:39, 1945. (*f*) Easton, W. H.: Carbon Tetrachloride in Industrial Hygiene, Indust. Med. **12**:1, 1943. (*g*) Eddy, J. H., Jr.: Carbon Tetrachloride Poisoning in Industry, ibid. **14**:283, 1945. (*h*) Gaultier, C.; Chatron, M., and Seidmann, P.: Carbon Tetrachloride Intoxication, Bull. et mém. Soc. méd. hôp. Paris **49**:1638, 1933. (*i*) Gocher, T. E. P.: Carbon Tetrachloride Poisoning, Northwest Med. **43**:228, 1944. (*j*) Lehman, K. B., and Flury, F.: Toxicology and Hygiene of Industrial Solvents, Baltimore, Williams & Wilkins Company, 1943.

Case 3 represents an instance of severe psychiatric disturbance with evidence of diffuse toxic encephalopathy associated with peripheral neuritis. An unusual feature was the delayed onset of the neuropsychiatric syndrome.

Case 3.—A man aged 39, a social drinker, while cleaning his gun with carbon tetrachloride in a closet, drank two highballs. The following evening he had abdominal pain, and the next day polyuria, nausea, vomiting, and restlessness appeared. Four days after exposure he was admitted to Georgetown University Hospital, where small conjunctival hemorrhages were observed in the left eye. The neurological examination was negative, but on the 10th day he became lethargic, with associated uremia, hyperkalemia, and hypertension. The uremia and high blood pressure resolved and the patient improved in general, but on the 18th day after exposure he became euphoric, and diplopia, marked ataxia, and visual hallucinations developed. Neurological examination showed absence of position sense, weakness and hyporeflexia of both lower extremities, marked confusion, disorientation, and incontinence. The sensory status was virtually impossible to evaluate. The impairment of position sense was so gross, however, that he was unable to locate his own extremities. It was felt that the patient had a peripheral neuritis on the basis of his carbon tetrachloride poisoning. A few days later it was apparent that the Babinski sign was developing. This was feeble at first, but from day to day it became more active. The knee and ankle jerks returned, at first being feeble, and then gradually increasing, so that within 10 days they were very hyperactive and within three weeks persistent bilateral ankle and knee clonus had developed. The upper extremities were also effected, and marked grasp reflexes developed bilaterally, more marked on the right, with the usual response to postural changes. During this period he remained confused and disoriented as to time, place, and position. No gross visual field defects were apparent. The spinal fluid was normal. An electroencephalogram was borderline, with a considerable amount of slow activity.

There was gradual improvement, and the patient was discharged from the hospital after 84 days. He was still greatly confused and somewhat euphoric, and he had lost his mathematical ability. His judgment was impaired, and there was a personality slump, characterized by unawareness of his predicament and fatuous imperturbability. The previously familiar routine operation of his business had to be completely and painstakingly relearned, as though he were a new apprentice. Six months after discharge from the hospital, he was admitted to the accident ward because of convulsive seizure. This was his first and only major seizure; but, on being questioned, he volunteered that he had had episodes of feeling dizzy, followed by a sensation of strangeness or unreality. Occasionally in these episodes he would mumble or say something which he did not recall later. In other words, he demonstrated typical phenomena of a temporal lobe seizure, and an electroencephalogram at the time showed a spiking focus in the temporal lobe (Fig. 1).

The clinical picture of encephalomyelitis was particularly well demonstrated in the last case. It was characterized by mental aberration, intellectual defects, pyramidal tract signs, and loss of vibratory sense. With the gradual evolution of the full clinical pattern of encephalomyelitis, there developed permanent hemiplegia, with pyramidal tract signs and a bilateral grasp reflex, which eventually disappeared. The mechanism by which this occurs is not clear. There are two possibilities: One is a coexisting hematomyelia, which is suggested by the subconjunctival hemorrhages that the patient had. Another is a direct or an indirect demyelination, due to the effect of carbon tetrachloride itself. That demyelination can occur is indicated in our pathological studies.

Damage to the cerebral cortex is, of course, suggested by the known narcotic effect of carbon tetrachloride. Permanent cortical destruction is suggested by the conspicuous psychiatric syndrome, and, as noted, other authors have reported mental changes. In Case 3 there was a long-continuing mania. Thus, in addition to the signs of myelitis, the patient had an encephalopathy from which he very slowly, and only partially, recovered. There also developed focal convulsive seizures of major type

and psychomotor seizures, and a temporal lobe focus was demonstrated. This constellation of organic mental syndrome, neurological signs, seizures, and an abnormal electroencephalographic pattern makes it obvious that cortical damage occurred in this case.

Cerebellar Degeneration: The pathological studies, mentioned later, show very clearly that the cerebellar cortex may also be involved. We have found no persistent cerebellar signs in our patients who survived, nor is there any description of a cerebellar degeneration clinically evident in the other reports in the literature. It may well be that cerebellar damage occurs only in those patients so severely intoxicated that they are unable to recover.

Peripheral Neuritis: Only a few, and usually casual, references to peripheral neuritis can be found in the literature.[14] Paresthesias or pain, as in Case 1, is often the only manifestation. In 1940 Hagen and associates [16] noted numbness of the extremities in a patient, and Farrell and Senseman [15] described a soldier with polyneuritis due to absorption of carbon tetrachloride through the skin. Weakness

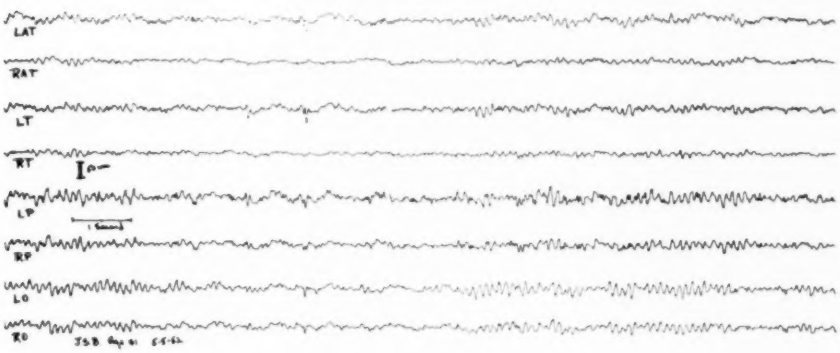

Fig. 1 (Case 3).—Electroencephalogram six months after carbon tetrachloride intoxication. Moderate voltage spiking discharges occur in the left temporal, anterior temporal, and parietal regions.

in his legs, pain in the calves, and numbness in the fingers and hands appeared first. The weakness finally involved all limbs, and he was unable to rise from the squatting position or stand on his heels or toes. The deep reflexes were decreased, and the ankle jerks were absent.

In animals exposed to various concentrations of carbon tetrachloride, Smyth, Smyth, and Carpenter [41] found definite damage to the sciatic nerve, as demonstrated by dense clumps of black osmic-acid-stained material paralleling the large majority of fibers, and sometimes encircling them. The degree of damage was roughly correlated with the amount of exposure.

Optic Neuritis: In addition to peripheral neuritis, optic neuritis may occur after exposure to carbon tetrachloride and apparently is an early and sensitive sign of

14. (*a*) Dillenberg and Thompson.[13e] (*b*) Easton.[13f] (*c*) Lehman and Flury.[13j] (*d*) Lowdry, J.: Chronic Poisoning with Carbon Tetrachloride, Arch. Gewerbepath. u. Gewerbehyg. **6**:157, 1935.

15. Farrell, C. L., and Senseman, L. A.: Carbon Tetrachloride Polyneuritis, Rhode Island M. J. **27**:334, 1944.

chronic carbon tetrachloride toxicity.[16] Blurring of vision occurred in Case 3, but the visual fields and funduscopic appearance were normal. Cases of amblyopia due to this intoxicant have been reported by Wirtschafter,[16i] Gocher,[13i] Gray,[6d] and Smith.[16b] Routine perimetric examinations are recommended[16i] for detection of early signs of poisoning. Optic nerve degeneration in animals has been produced experimentally with carbon tetrachloride.[6i]

II. *Hemorrhagic Diathesis.*—This is a frequent phenomenon in carbon tetrachloride poisoning. In our 15 cases, it was found to range in severity from subconjunctival hemorrhages and echhymosis of the skin to severe bleeding from the gastrointestinal tract. Probably the acute liver damage is responsible. The prothrombin level is altered, and fibrinogen is decreased. Adams and associates[12] found a marked increase in plasma prothrombin-clotting time in rats and rabbits exposed to carbon tetrachloride. The clotting mechanism may be disturbed further by a low serum calcium content, often a concomitant of carbon tetrachloride intoxication.[17]

The central nervous system may become the site of spontaneous hemorrage,[18] and Fairhall[16g] states that in cases of fatal poisoning from high concentration autopsy shows cerebral hemorrhage and edema, pulmonary edema and emphysema, and, occasionally, a grossly enlarged liver.

Hypertension probably superimposes further vulnerability to intracranial hemorrhage.

Hemorrhage, as a mode of cerebral damage, was illustrated by Case 4.

Case 4.—J. J., a man aged 46, nonalcoholic, on Dec. 17, 1950, swallowed 2 tbsp. of carbon tetrachloride, mistaking it for 666 (a preparation of antipyrine, citric acid, Mg SO_4, and NH_4Cl). Two days later pain in the abdomen developed and progressed. One week later hematuria and melena appeared. Two days after that he became confused, and he was admitted to Gallinger Municipal Hospital on Dec. 27. Flaccidity of the right arm was noted, and there were subconjunctival hemorrhages in the left eye. There was a 2+ nuchal rigidity, and the spinal fluid was grossly bloody. Coma deepened, and the patient died on Dec. 28.

III. *Cerebral Fat Embolism.*—In addition to the direct neurotoxic effect and the hemorrhagic insult suffered by the brain in carbon tetrachloride poisoning, it is possible that damage may be imposed by cerebral fat emboli. This is entirely speculative, since neither we nor other investigators have yet demonstrated free fat in human nerve tissue. However, certain observations make it plausible that fat embolism may account for some of the clinical pathology. For example, multiple fat emboli have been found in the lungs of a patient poisoned by carbon tetrachloride.[19]

16. (*a*) Foxell.[16b] (*b*) Smyth, Smyth, and Carpenter.[6i] (*c*) Kugel.[8e] (*d*) Gocher.[13i] (*e*) Lehman and Flury.[13j] (*f*) Lowdry.[14d] (*g*) Fairhall, L. T.: Industrial Toxicology, Baltimore, Williams & Wilkins Company, 1949. (*h*) Smith, A. R.: Optic Atrophy Following Inhalation of Carbon Tetrachloride, Arch. Indust. Hyg. **1**:348, 1950. (*i*) Wirtschafter, Z. T.: Toxic Amblyopia and Accompanying Physiological Disturbances in Carbon Tetrachloride Intoxication, Am. J. Pub. Health **23**:1035, 1933.

17. Doyle, W. E., and Baker, C.: Carbon Tetrachloride Poisoning Epidemic in Parachute Plant, Indust. Med. **13**:184, 1944.

18. Etienne and Martin: A Case of Carbon Tetrachloride Intoxication, Arch. Gewerbepath. u. Gewerbehyg. **5**:208, 1934. Hayhurst, E. R.: Proceedings of the 8th International Congress for Accidental & Industrial Diseases, Leipzig, 1938, p. 1180.

19. Lehnherr, E. R.: Acute Carbon Tetrachloride Poisoning: Report of a Case, Arch. Int. Med. **56**:98, 1935.

Rosenthal and Lillie [20] produced hyperlipemia in dogs by feeding them carbon tetrachloride. This hyperlipemia caused further impairment of liver function.

Butsch [21] found 1,245 mg. of fat per 100 cc. in the blood and 865 mg. of cholesterol per 100 cc. in a patient with carbon tetrachloride poisoning. The hyperlipemia receded, with clinical improvement.

The obese seem more vulnerable to the toxic effects of carbon tetrachloride.[22]

MacMahon and Weiss [23] report a fatal case of carbon tetrachloride poisoning in an alcoholic who drank an ounce of Carbona. At autopsy, six hours after death, blood was aspirated from the pulmonary artery and placed in a graduated cylinder. In a few minutes fat floated to the surface of the graduate and solidified. This blood contained 64% fat. Blood from the inferior vena cava contained 25% fat. In studies of the systemic circulation, fat was seen in the vessels of nearly all organs in minute droplets. However, histopathological investigation of the brain, including fat stains, revealed no abnormal deposition of fat.

PATHOGENESIS

Human and experimental neuropathological and neurophysiological studies are too meager to permit any definite deductions regarding the pathogenesis of carbon tetrachloride intoxication. There is a corresponding paucity of data on the metabolism and the fate of carbon tetrachloride in the body. Some inferences may be drawn by comparison with the effect of other chlorinated methanes.[11] Carbon tetrachloride has the promptest and most profound depressant effect on the medullary centers, with corresponding lowering of the blood pressure, heart and respiratory rates, and body temperature. The relatively greater accumulation of carbon tetrachloride in the brain parallels its greater oil-partition coefficient, and partition coefficient for oleic alcohol over water, and corresponds also to its greater narcotic action. These characteristics account for the shock-like state produced by acute carbon tetrachloride intoxication.

The precise mode of action and fate of carbon tetrachloride in the body are unknown, but it appears that it is metabolized. McCollister and his co-workers,[24] using C^{14}, found that 10 to 20% of the total radioactivity in the blood and expired air of animals fed C^{14}-labeled carbon tetrachloride was present in the form of $C^{14}O_2$. C^{14} was identified in urinary urea and carbonates, but the chief metabolic product in urine was unidentified, nonvolatile material, found to have attributes suggestive of a conjugate.

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20. Rosenthal, S. M., and Lillie, R. D.: Functional and Histologic Study of the Effect of Fat Ingestion upon Normal and Damaged Livers, Am. J. Psysiol. **97**:131, 1931.

21. Butsch, W. L.: Cirrhosis of the Liver Caused by Carbon Tetrachloride, Clinical Notes, J. A. M. A. **99**:728, 1932.

22. Guichard, A.; Cortet, and Roche, L.: Fatal Carbon Tetrachloride Intoxication, Arch. mal. profess. **9**:55, 1948. Eddy, J. H.: Carbon Tetrachloride Poisoning: A Preliminary Report on the Use of Methionine in Hepatitis, J. A. M. A. **128**:994, 1945.

23. MacMahon, H. E., and Weiss, S.: Carbon Tetrachloride Poisoning with Macroscopic Fat in the Pulmonary Artery, Am. J. Path. **5**:623, 1929.

24. McCollister, D. D.; Beamer, W. H.; Atchison, G. J., and Spencer, H. C.: Studies with Low Vapor Concentrations of Carbon Tetrachloride Labeled with Carbon 14: I. Absorption, Distribution, and Elimination upon Inhalation by Monkeys, Federation Proc. **9**:390, 1950.

Some authorities have suggested that carbon tetrachloride is toxic by virtue of its forming phosgene. But high temperatures are necessary to produce phosgene from carbon tetrachloride, and no such mechanism has been identified in the body. However, it is possible, e. g., that when carbon tetrachloride fire extinguishers are used, the heat of the burning material may convert some of the carbon tetrachloride to phosgene. Such a phenomenon was probably effected when the crew of a submerged submarine was exposed to carbon tetrachloride fumes which were in contact with heating units in the galley.[25] A similar instance was recorded during World War II, in which a group of workers became ill after cleaning hot metal with carbon tetrachloride-soaked rags.

Another explanation for the effects of carbon tetrachloride on the central nervous system is proposed by Minot.[26] She considers the elevated blood guanidine and guanidine-like substances responsible for the phenomena referable to the gastrointestinal tract and central nervous system. Guanidine is also implicated in the hypoglycemia sometimes found in carbon tetrachloride poisoning. When guanidine is injected into normal experimental animals, lethargy and other central nervous system signs are produced. By injection of calcium, which allegedly antagonizes guanidine, the central nervous system signs resolve, and the hypoglycemia is combated. The latter effect is produced through the mechanism of increased glycogenolysis. Calcium gluconate also was found to protect dogs from chloroform poisoning. Cantarow and associates[27] also found that the number of fatal poisonings in cats was diminished if calcium was administered. He attributed this beneficial effect to slighter impairment of liver function and less hepatocellular damage when calcium was employed.

Whatever the mechanism, the consensus is that calcium diminishes the severity of carbon tetrachloride intoxication and is indicated in treatment. Conversely, low calcium in humans or animals tends toward increased toxicity.[17]

In this connection, fat, like alcohol, if ingested at the time of exposure to carbon tetrachloride, potentiates the effect.[28] This is probably due to increased absorption, since fat acts as a vehicle conveying the poison into the lymphatics and directly to the thoracic duct, thus circumventing the liver, which might partially detoxify or mollify the effect of carbon tetrachloride poison.[29]

When dogs are fed carbon tetrachloride with cream, the animals show incoordination and nervous symptoms that are never present when the drug is taken into an empty intestine.[5] The amblyopia occasionally found in carbon tetrachloride poisoning resembles other forms of optic neuritis due to toxins, and it has been

25. Carbon Tetrachloride Poisoning, U. S. Nav. M. Bull. **43**:396, 1944.

26. Minot, A. S.: Mechanism of Hypoglycemia Produced by Guanidine and Carbon Tetrachloride Poisoning and Its Relief by Calcium Medication, J. Pharmacol. & Exper. Therap. **43**:295, 1931.

27. Cantarow, A.; Stewart, H. L., and Morgan, D. R.: Experimental Carbon Tetrachloride Poisoning in the Cat: Influence of Calcium Administration, J. Pharmacol. & Exper. Therap. **62**:153, 1938.

28. Clinton, M.: Carbon Tetrachloride, Am. Petrol. Inst. Toxical Rev., Sept., 1948, pp. 1-6.

29. Geraghty and Rogers.[4e] Lamson and Wing.[4g] Burns, C. R.: Carbon Tetrachloride Poisoning: Report of a Case with Unusual Features, New Zealand M. J. **45**:291, 1946.

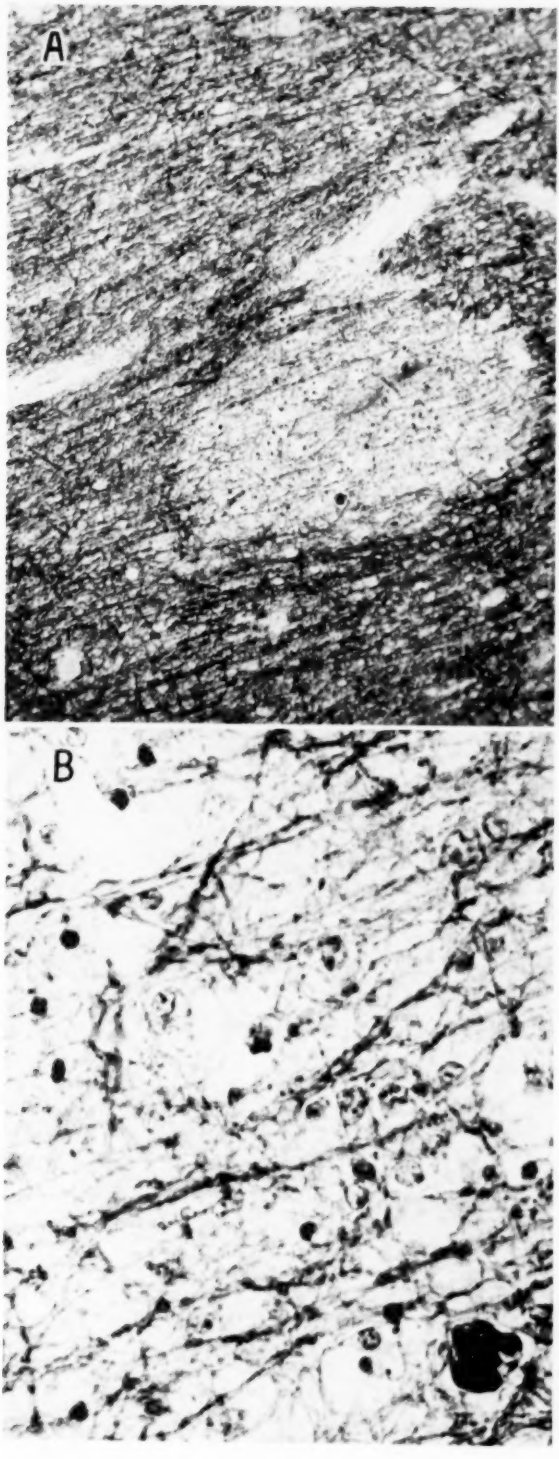

Fig. 2—Weil-stained sections of cerebral white matter of case J. R. *A* perivascular area of demyelination; ×100. *B*, phagocytic changes in area of demyelination; ×600.

suggested that this visual disturbance may be induced by the effect of the deranged fat metabolism on the visual purple of the rods, and that further alterations in retinal metabolism result from glucose deprivation secondary to the low blood sugar often found in carbon tetrachloride poisoning.[161]

PATHOLOGY

Histological studies of the nervous system of patients who die of carbon tetrachloride poisoning are extremely meager, and it is impossible to conclude that our

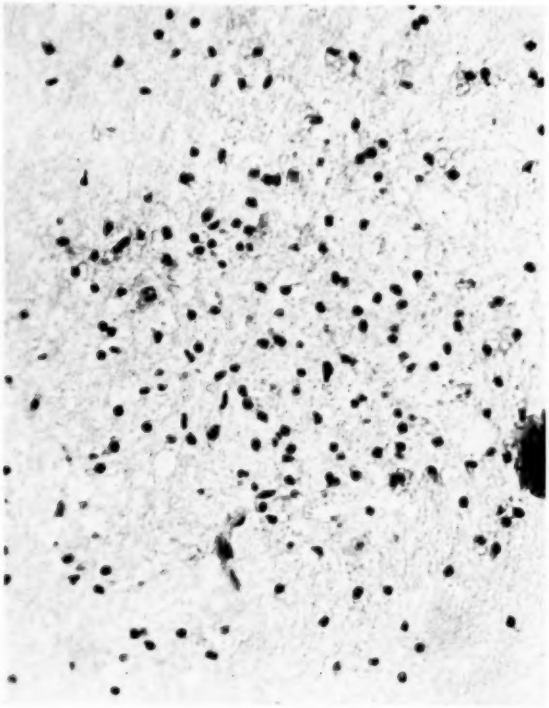

Fig. 3.—Perivascular glial nodule in carbon tetrachloride poisoning. Hematoxylin-eosin stain; × 100.

neuropathological findings are necessarily representative. Autopsy material was obtained from two patients. The first, J. R., a man aged 29, while drunk cleaned a sofa with carbon tetrachloride-containing fluid in a poorly ventilated room. He died on Dec. 3, 1951, two days after admission to the Mount Alto Veterans Administration Hospital.

Histological examination of the brain showed scattered small areas of demyelination with necrosis. These were extremely well demarcated, and were usually associated with blood vessels and in the white matter of the cerebral cortex. In these areas of demyelination were cellular debris and gitter cells, some laden with fat

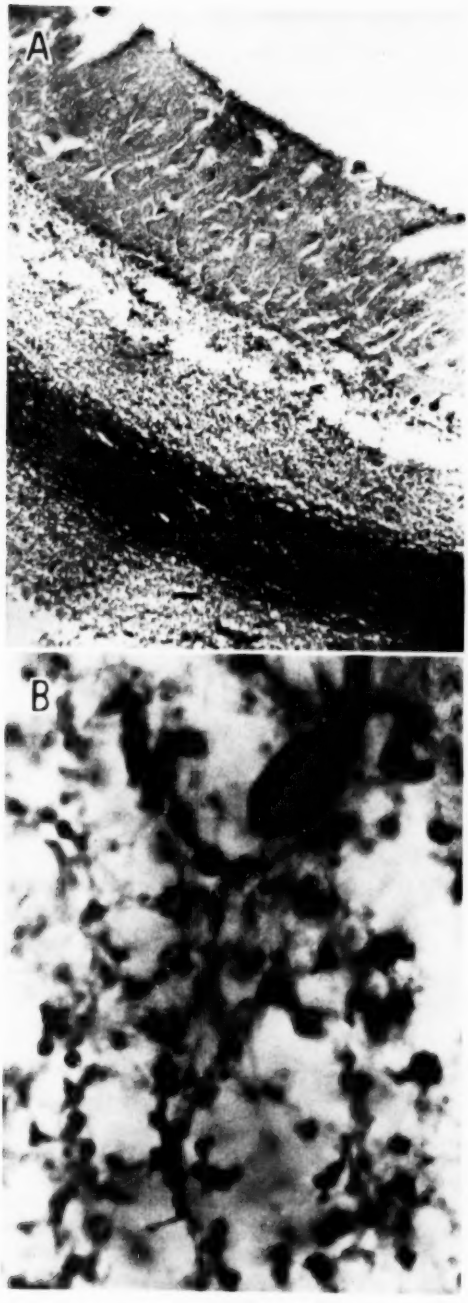

Fig. 4.—*A*, cerebellum in acute carbon tetrachloride poisoning, showing marked loss of cells in granular layer and paucity of Purkinje cells; × 70. *B*, same section, showing pyknosis of Purkinje cells and paucity of granular cells; × 980.

and pigment (Fig. 2). This is evidence of an acute necrotic lesion, of perivenous type, marked by demyelination and an attempt at phagocytic removal of debris. Lesions such as this are not unlike those of the acute perivenous encephomyelitides, and there may well be a demyelination similar to this. The possibility of fat embolism does not seem likely here, although it could not definitely be ruled out. Glial nodules (Fig. 3) were also present. These findings suggest the changes produced in rabbits by Biancalani,[30] who poisoned dogs and rabbits with carbon tetrachloride and on examining the brain found a variety of prominent, nonspecific changes, including glial proliferation, particularly in perivascular areas.

The other patient, an alcoholic aged 36, washed machinery parts in carbon tetrachloride. After four days he had onset of "dizziness" and pain radiating down his legs. On April 27, 1951, he was admitted to the Mount Alto Veterans Administration Hospital with hemoptysis. He died on May 4.

The neuropathological changes were histological in type, and the abnormalities were limited to the cerebellum (Fig. 4). Unfortunately, however, the peripheral nerves in this case were not available. In the cerebellar cortex the molecular layer was strikingly disorganized, with a conspicuous falling out of neuronal elements. Purkinje cells were pyknotic and greatly decreased in number. This change was primarily a neuronal effect, for there was no glial response or frank necrosis.

The latter findings are suggestive of similar cerebellar lesions produced experimentally by the Japanese workers.[31] They poisoned dogs fatally with carbon tetrachloride and noted that the animals exhibited anorexia, lethargy, generalized weakness, incoordination, and sialorrhea before they died.

The cerebellum, particularly in the molecular and Purkinje layers, showed fresh hemorrhages. Purkinje cells were decreased in number; many were pale, pyknotic, and misshapen.

TREATMENT

The treatment of carbon tetrachloride poisoning has been outlined in several recent articles.[32] In general, therapeutic efforts are directed toward lavaging the stomach and combating shock and narcosis. Epinephrine and similar drugs are contraindicated. The later complications of renal and hepatic damage, hemorrhagic diathesis, and uremic convulsions are treated symptomatically in the conventional manner. Peritoneal lavage and use of the artificial kidney are drastic measures, which have not yet been evaluated.

30. Biancalani, A.: Experimental Research on the Alterations of the Central Nervous System in Intoxication by Carbon Tetrachloride, Riv. pat. nerv. **44**:352, 1934.

31. Tanohata, K., and Tagawa, D.: Histopathologic Study of Central Nervous System in Experimental Carbon Tetrachloride Poisoning, Nagasaki Igakkai Zassi **10**:1505, 1932.

32. Farrier and Smith.[1a] Myatt and Salmons.[1b] Allison.[1g] Case 34221.[1j] Baggenstoss, A. H.: Carbon Tetrachloride Intoxication Treated by Peritoneal Lavage: Pathologic Aspects, Proc. Staff Meet., Mayo Clin. **22**:321, 1947. Recognition and Treatment of Carbon Tetrachloride Poisoning, Report of Council on Industrial Health, J. A. M. A. **132**:786, 1946. Davis, G. G., and Hanelin, H. A.: Carbon Tetrachloride Poisoning: Outline of Successful Treatment, Indust. Med. **6**:24, 1937. Snell, A. M.: Carbon Tetrachloride Intoxication Treated by Peritoneal Lavage: Clinical Aspects, Proc. Staff Meet., Mayo Clin. **22**:367, 1947. Poisoning Due to Substances Commonly Substituted for Ethyl Alcohol, Veterans Administration Technical Bulletin, 10-89, 1953.

SUMMARY

Carbon tetrachloride is a common household article whose danger as a potentially lethal intoxicant has not been advertised sufficiently. Labeling of the container should be similar to that for other poisons, and the public should be educated regarding the deadly potency of the fluid. A single exposure can be fatal.

Alcohol imbibed during exposure greatly increases the toxicity of carbon tetrachloride, a fact that should also be better known.

Acute carbon tetrachloride poisoning is dominated by symptoms of the central nervous system, such as headache, diplopia, incoordination, paresthesias, impaired vision, confusion, and coma.

An etiological classification is tabulated.

Reports of neurological aspects of carbon tetrachloride intoxication are extremely meager, incomplete, and scattered.

A total of 15 cases of carbon tetrachloride poisoning are reported and typical ones cited. Neuropathological findings are described, and the literature is reviewed.

FACTORS INFLUENCING EXTENSOR TONUS AND RESPIRATION IN DECEREBRATE CATS

W. D. HAGAMEN Jr., M.D.
AND
R. L. BEALS, A.B.
NEW YORK

IN THE process of decerebrating a number of cats, it was noticed that there was considerable variation in the degree of extensor tonus which developed. With continued practice and standardization of the operative technique, the variability in the immediate postoperative period was made very slight. However, in animals observed an hour or more after operation, the degree of extensor tonus varied tremendously from one cat to another. Moreover, in any one cat there were usually transitory, but very marked, changes in tonus which could not be readily explained by means of known reflex patterns.

In one of the decerebrate cats a Cheyne-Stokes type of breathing developed. During periods of apnea the extensor tonus was slight to moderate, and during periods of breathing the cat went into pronounced opisthotonos. This suggested that factors which were capable of influencing respiration might also influence extensor tonus. The purpose of the present paper is to investigate this possible relationship.

METHODS

Fifty-three cats were decerebrated, 42 by the anemic method and 11 by transection. The technique of Pollock and Davis [1] was modified by the use of a parapharyngeal approach and by occlusion of the basilar artery with brain clips. Sometimes the basilar artery and the carotid arteries were occluded at the same time, and sometimes the basilar artery was clipped days or weeks earlier. The complete operation takes from 10 to 30 minutes. Thiopental sodium (Pentothal sodium), given intravenously, was used as the anesthetic in all operations. A tracheal cannula was often inserted as a ready means of occluding the airway. In an attempt to estimate the level and the completeness of functional transection, some of the cats were perfused with isotonic sodium chloride solution, followed by a mixture containing 10% formaldehyde and 25% India ink, at a pressure of 200 mm. Hg. In order that the extensor tonus might be estimated, the cats were suspended by strings through the interspinous ligaments between the first and the second thoracic and the fourth and the fifth lumbar vertebrae.

RESULTS

The great majority of the cats went into opisthotonos immediately after clamping of the basilar artery. Failure to do so seemed to be a sign of a deeper level of anesthesia. This exaggerated extensor tonus lasted less than one minute. After

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This study was aided by a fellowship to Dr. Hagamen from the National Foundation for Infantile Paralysis, Inc.

1. Pollock, L. J., and Davis, L. E.: Studies in Decerebration: I. A Method of Decerebration, Arch. Neurol. & Psychiat. **10**:391-398, 1923.

this the extensor tonus could be described as moderate. The cats did not support their heads and tails against gravity, or did so only partially (Fig. 1). The legs could partially support themselves against gravity (Fig. 2). The extensor tonus was always greater in the forelegs than in the hindlegs and was greater in the neck than in the tail.

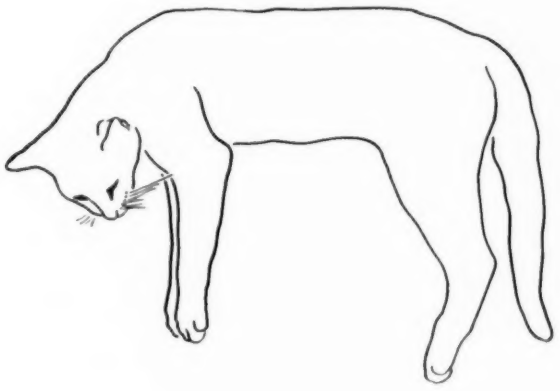


Fig. 1.—Decerebrate cat suspended, showing normal tone. Temperature 39 C.; respiration rate, 24 a minute. This figure and the accompanying figures are traced from photographs of the same cat.

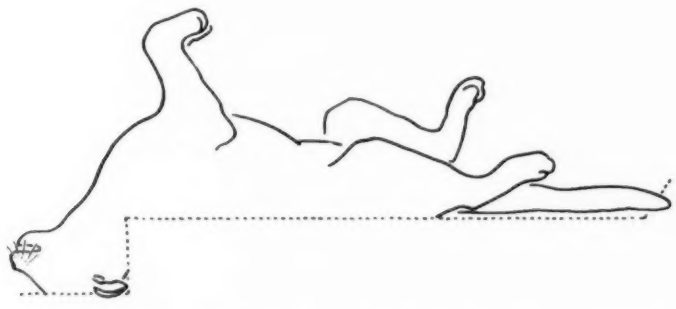


Fig. 2.—Decerebrate cat lying on its back, showing normal tonus. Temperature, 39 C.; respiration rate, 24 a minute.

Suffocation.—Complete clamping of the cat's airway always produced a definite sequence of events. The cat would exhibit very labored respiratory movements. These were often accompanied by flexing movements of the trunk, neck, and extremities. The tail would lash back and forth. After this the cat went into very marked extension. Increasing extension was first noticeable in the forelegs and neck, and then in the hindlegs, tail, and back. As the extensor tonus was increasing, both tendon reflexes and withdrawal reflexes were increased.

When extension was maximum, the cat was in extreme opisthotonos. The chin, the ventral surface of the neck, and the forelegs were almost in a straight line. The spine was arched, and the tail lay along the back. The hindlegs were at first pointed somewhat backward (hip extended), and then parallel to the forelegs (hip flexed), but were always rigidly extended at the knee (Figs. 3 and 4). The wrist joints

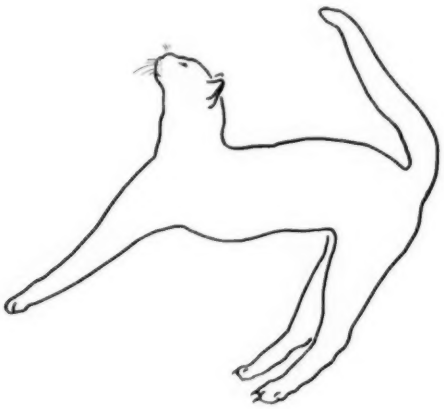


Fig. 3.—Decerebrate cat suspended, showing marked opisthotonos immediately after removal of a clamp from the airway. Temperature 39 C.

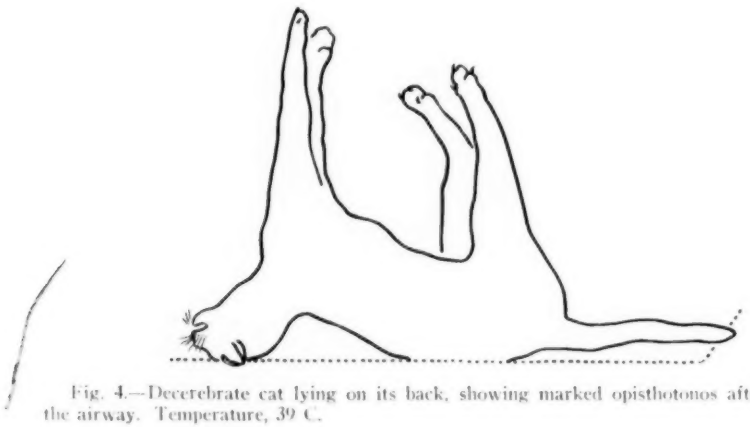


Fig. 4.—Decerebrate cat lying on its back, showing marked opisthotonos after clamping of the airway. Temperature, 39 C.

were less completely involved in this extension. When extension was complete, tendon reflexes could not be demonstrated, possibly because of already maximum contraction of the extensors.

Withdrawal reflexes were also absent during maximal opisthotonos except for what may be called a "paradoxical flexion response." When a strong electric stimulus was applied to the foot pad of an otherwise unstimulated decerebrate cat,

all the joints of the extremity flexed. However, during an extensor spasm the wrist joints were apparently the only ones free to move. This often resulted in the foot pad being pushed harder against the electrodes.

The time between clamping the airway and the development of maximum opisthotonos varied from 30 to 150 seconds (perhaps partly owing to variations in the amount of leakage around the tracheal cannula). After the first evidence of increasing extensor tonus, it was only 10 to 30 seconds before full extension was reached. The clamp was usually removed within 30 seconds after extreme opisthotonos had developed; otherwise the animal would relax and die. After removal of the clamp, the animal would usually begin to relax and have a return of reflexes within 10 to 30 seconds, but occasionally would remain in extreme opisthotonos for several minutes. The clamp was not left on long enough to produce piloerection of the tail, but occasionally urination would occur.

We shall call the condition of maximum opisthotonos and associated features described above a "decerebrate extensor spasm." Clamping of the airway in a normal cat or a decorticate cat produces flexion and thrashing, but no opisthotonos.

Periodic Breathing.—Five cats exhibited a Cheyne-Stokes type of respiration. Each cat had a very definite increase in extensor tonus during the periods of breathing and a decrease during the periods of apnea. A description of one of these cats follows.

The animal had respiratory cycles of 35 to 40 seconds. There would be four to six very deep respirations, during which extreme opisthotonos, lasting 12 to 15 seconds, would develop. This would be followed by a period of apnea, lasting 23 to 25 seconds, during which time the cat would have only moderate extensor tonus. Thirty-five to 40 seconds after the onset of the first inspiration the cycle would be repeated. These cycles were repeated with almost perfect rhythmicity for the period of immediate observation, i. e., 30 minutes.

Pinching the forepart of the cat's body (forelegs, ears, or mouth) would produce a single (occasionally two) deep inspiration. A slightly increased extension of the forelegs could also often be observed. If the cat was pinched at approximately 20-second intervals, the cycle described above could be inhibited for periods up to 5 minutes, i. e., as long as it was attempted. When the pinching was stopped, the cat would eventually reestablish the cycles—first, only the respiratory movements, in cycles increasing from 20 to 35 seconds. When a 35-second interval was reached, the opisthotonos would appear as part of the cycle, as described above.

Chemical Stimuli.—Various chemicals or mixtures which are known to stimulate respiration were tested for their effects upon extensor tonus. A 7% CO_2 and 93% O_2 mixture, a 9% CO_2 and 91% O_2 mixture, and 100% N_2 were all given to different cats at atmospheric pressure without rebreathing. Each mixture, when given for a period sufficient grossly to stimulate respiration, also produced a decerebrate extensor spasm identical in every respect to that described previously. Two cubic centimeters of a saturated solution of NH_4Cl was given intravenously to four cats. This markedly stimulated both the rate and the depth of respiration and produced a very severe decerebrate extensor spasm.

Body Temperature.—The body temperature was found to be one of the most important variables determining the amount of extensor tonus in the cats. The quickness with which, and the extent to which, the other stimuli increased extensor tonus were dependent to a large degree upon the body temperature. The rectal temperatures of our preoperative cats when taken from the cage averaged 39.0 C. (102.2 F.). If the temperature was low enough, e. g., somewhere below 36 C.

(96.8 F.), the degree of extensor tonus produced by clamping the airway was less than usual. If the temperature was very low, no increased tonus was produced. As the temperature rose, it became easier to produce opisthotonos. At temperatures between 40 and 42 C. (104 and 107.6 F.) very minor stimuli, such as turning the animal over, moving him from the floor to table, or pinching him, would all precipitate a decerebrate extensor spasm. If the temperature was high enough, usually about 42 to 43 C. (107.6 to 109.8 F.), the cat was likely to be in continuous opisthotonos. The respiration of the cats was very sensitive to temperature, both the rate and the depth increasing with increased body temperature.

Other Stimuli.—Electrical stimulation of the sciatic nerve sufficient to stimulate respiration grossly would very consistently produce opisthotonos. Except for the position of the stimulated leg, this opisthotonos was identical in all respects with the decerebrate extensor spasm described previously.

As mentioned in the discussion of body temperature, various very minor mechanical stimuli would, when the body temperature was sufficiently high, produce decerebrate extensor spasms.

Deafferentation.—Several cats had the dorsal roots cut on one side, from the fourth cervical to the second thoracic, inclusive, several weeks before decerebration. The deafferented limb was flaccid after decerebration. However, when opisthotonos had developed, the deafferented limb was as rigid as the other limbs. In fact, the extensor tonus increased at an obviously greater rate in the deafferented limb than in the normal limbs. However, the deafferented limb was always areflexic.

COMMENT

This work seems to suggest that the physiological condition of the animal should be carefully considered in any experiments on decerebrate animals in which the degree of extensor tonus is important. Many of these occasionally uncontrolled physiological factors are capable of influencing the extensor tonus as much as, or more than, some of the experimental lesions or procedures. The effect of deafferentation on extensor tonus is a good example, for the result could be either a flaccid limb or an extremely rigid limb, depending upon the condition of the animal.

Since the decerebrate cat is so universally described in physiology textbooks, and so commonly prepared in student laboratories, we should like, from the teaching standpoint, to suggest that there is a discrepancy between the decerebrate cat one usually obtains and the textbook picture, i. e., a cat in opisthotonos. We suspect that many are the students who have been somewhat embarrassed by the failure of their preparation to show opisthotonos, or unjustly proud because it did. The assumption that the greater the extensor tonus the better the technique is not necessarily valid. A cat in extreme opisthotonos would seem to be a very abnormal one. Such a cat is likely to have fever, acidosis, or a partially occluded airway. The reflexes so characteristic of a normal decerebrate cat cannot be demonstrated in extreme opisthotonos.

It is important to remember that there are varying degrees of opisthotonos. A cat which shows opisthotonos while lying on its side may well not have anywhere near the strength necessary to support its head when it is suspended by the interspinous ligaments.

The role of the body temperature holds a unique place among the factors discussed because it has such a strong influence and is so labile, but still is easily measured and controlled. It also easily accounts for some of the long-sustained variations in tonus, not decerebrate extensor spasms alone. The usual temperature of the cat immediately after operation was 37 C. If the temperature of the room was low, the body temperature would continue to fall. If the temperature of the room was high, the body temperature would begin to rise. Animals in which the carotid arteries were not tied until the next day tended consistently to be more rigid because most of them had enough infection to give them a fever.

It is tempting to speculate here on the anatomical overlap of Magoun's facilatory area [2] and the respiratory center.[3] However, it does not seem fair to deduce that our results are actually dependent upon such a relationship. The factors considered here as respiratory stimuli can probably, under the proper conditions, stimulate all parts of the central nervous system. The literature relating to this point is very extensive, and it does not seem appropriate to review it here. However, it may be worth noting that as long ago as 1910 Mathison [4] showed that lack of oxygen and injection of acids have a marked stimulating effect on the spinal animal. Otherwise, we shall limit ourselves to a discussion of the work actually concerned with the decerebrate state.

It is interesting that more information relating to our thesis is to be found in the clinical than in the experimental literature. There is repeated reference to what is called "tonic fits" in cases of lesions of the brain stem, in some of which the patient appears to be truly decerebrate. A tonic fit is usually a brief extensor spasm with opisthotonos and is often associated with changes in respiration. It seems to be very similar to what we called decerebrate extensor spasms in our cats.

One of the first such references is one by Wilson [5] in 1920. King [6] reports two cases. In one of these hypernea, a temperature of 105 F., and almost any form of stimulus would produce opisthotonos. In the other the temperature was 102.8 F., and strong pinching of any part of the body would produce a deep breath and a tonic fit. Epstein and Yakovlev [7] report a case in which sudden external stimuli produced opisthotonos with a deep inspiration, even though there was not loss of consciousness. Walshe [8] also had a case with tonic fits and respiratory crises in which there was an elevated body temperature. He states that the patient became so

2. Magoun, H. W., and Rhines, R.: Spasticity: The Stretch-Reflex and Extrapyramidal Systems, Springfield, Ill., Charles C Thomas, Publisher, 1947.

3. Pitts, R. F.; Magoun, H. W., and Ranson, S. W.: Localization of the Medullary Respiratory Centers in the Cat, Am. J. Physiol. **126**:673-688, 1939.

4. Mathison, G. C.: The Action of Asphyxia upon the Spinal Animal, J. Physiol. **41**:416-449, 1910.

5. Wilson, S. A. K.: On Decerebrate Rigidity in Man and the Occurrence of Tonic Fits, Brain **43**:220-268, 1920.

6. King, A. B.: Two Cases Showing Tonic Neck Reflexes and Tonic Fits Following Vascular Lesions in the Brain Stem, J. Nerv. & Ment. Dis. **92**:302-308, 1940.

7. Epstein, S. H., and Yakovlev, P. I.: A Case of Decerebrate Rigidity with Autopsy, J. Neurol. & Psychopath. **10**:295-304, 1930.

8. Walshe, F. M. R.: A Case of Complete Decerebrate Rigidity in Man, Lancet **2**:644-647, 1923.

rigid that tendon reflexes could not be elicited. Zand[9] mentions a case without autopsy in which pricking the chest produced a quickening of respiration and increased tonus. Bazett,[10] Walshe,[11] and Davis[12] believe that tonic fits are due to bleeding and irritation.

Bazett and Penfield[13] mention that their chronic decerebrate cats showed occasional tonic fits. One of the best descriptions we found of the variation in extensor tonus occurring in decerebrate cats was that of Porter,[14] although his discussion is almost limited to the tail muscles. Henderson and Sweet,[15] in the protocol of one of their cats, state that the legs showed increased tonus with descent of the diaphragm. Weed[16] found that applying warm (45 C.) saline solution to the cut surface of the midbrain increased extensor tonus and that application of cold (16 C.) saline decreased it. Namihisa[17] reports that increasing either the body temperature or the temperature of the cut surface of the brain stem in the decerebrate cat increased the "secondary part" of the knee jerk. Sherrington[18] points out that with increasing body temperature running movements were produced in decerebrate dogs by even light handling. (He was probably using a somewhat higher level of section here.) Rogers[19] notes a stimulating effect of increasing the body temperature in decerebrate pigeons, but the posture and activity of decerebrate pigeons are, of course, quite dissimilar to those of decerebrate cats.

The only dissenting paper we came upon was one by Stella.[20] He states:

> [Decerebrate cats] were placed either in full extension or passively flexed and allowed to remain so. Injection into the common carotid of cyanide or sulphide in quantity sufficient very markedly to stimulate reflexly respiration or apneusis seemed entirely without effect upon the position of the limbs, thus indicating that the centers for decerebrate rigidity are not appreciably affected by those afferent discharges which powerfully excite the respiratory and "apneustic" centers.

9. Zand, N.: Decerebrate Rigidity from a Clinical and Physiological Standpoint, J. Nerv. & Ment. Dis. **67**:105-119, 1928.

10. Bazett, H. C.: Discussion on Decerebrate Rigidity in Man and the Occurrence of Tonic Fits, Brain **43**:300-307, 1920.

11. Walshe, F. M. R.: The Decerebrate Rigidity of Sherrington in Man: Its Recognition and Differentiation from Other Forms of Tonic Muscular Contraction, Arch. Neurol. & Psychiat. **10**:1-28, 1923.

12. Davis, L. E.: Decerebrate Rigidity in Man, Arch. Neurol. & Psychiat. **13**:569-579, 1925.

13. Bazett, H. C., and Penfield, W. G.: A Study of the Sherrington Decerebrate Animal in the Chronic as Well as the Acute Condition, Brain **45**:185-265, 1922.

14. Porter, E. L.: Evidence That the Postural Tonus of Decerebrate Rigidity Increases in Amount by the Successive Innervation of Single Motor Neurones, Am. J. Physiol. **91**:345-361, 1929.

15. Henderson, V. E., and Sweet, T. A.: On the Respiratory Center, Am. J. Physiol. **91**: 94-102, 1929.

16. Weed, L. H.: Observations upon Decerebrate Rigidity, J. Physiol. **48**:205-227, 1914.

17. Namihisa, F.: Die Beziehung zwischen Körpertemperatur und Lebensfunktionen bei der enthirnten Katze: Ueber den Einfluss der Körpertemperatur auf den Sehnenreflex sowie ihre Wirkungslokalisation im Zentralnervensystem, Mitt. med. Gesellsch. zu Tokio **47**: 72-73, 1933.

18. Sherrington, C. S.: Notes on Temperature After Spinal Transection, with Some Observations on Shivering, J. Physiol. **58**:405-424, 1924.

19. Rogers, F. T.: Experimental Studies on the Brain Stem: III. The Effects on Reflex Activities of Wide Variations in Body Temperature Caused by Lesions of the Thalamus, J. Comp. Neurol. **31**:17-35, 1919.

20. Stella, G.: The Reflex Response of the "Apneustic" Centre to Stimulation of the Chemoreceptors of the Carotid Sinus, J. Physiol. **95**:365-372, 1939.

We did not use either cyanide or sulfide as a stimulus and at present are unable to explain this apparent discrepancy. However, the explanation may possibly be found in some physiological difference in our animals, such as a difference in temperature.

In a very interesting paper, Keller [21] points out that his decerebrate dogs were relatively atonic, rather than hypertonic. This is one of the few papers found in which it was suggested that, although the degree of tonus may vary, an optimal decerebrate animal may not be a rigid one.

Our observations on the effects of deafferentation would seem to indicate two things: 1. A large part, at least, of the moderate extensor tonus of the unstimulated decerebrate cat is due to afferent impulses from the extremities themselves, since the limb becomes quite flaccid after deafferentation.

2. The increased extensor tonus which we found after our various stimulations was purely central in origin, and not dependent upon afferent fibers from the limbs themselves.

These conclusions appear to be consistent with the literature as far as it is possible to tell. Sherrington [22] found that the deafferented limb was flaccid in a decerebrate cat, but we cannot, of course, determine the exact physiological condition of his cats. Liljestrand and Magnus [23] observed some rigidity in the deafferented limb. Pollock and Davis [24] found pronounced tonus in cats which had all the dorsal roots cut, but it is possible, although not stated, that their animals were warmer or were stimulated in some other way. Ranson [25] gives the most details, and thus his data are the easiest with which to compare our results. He says that some extensor tonus was always apparent in the deafferented limb, although it often did not appear for several hours, sometimes 24, after the decerebration. It is possible that this time was necessary for the temperature of his animals to rise somewhat. He states that this tonus was of an undulating nature and was central in origin, since the undulations were synchronous in all four extremities. He also points out that tonic neck and labyrinthine reflexes appeared brisker in the deafferented than in the control limbs. This statement would agree with our observation that in the production of a decerebrate extensor spasm the deafferented limb showed the increased tonus first.

Perfusion of the animals with India ink shows that, although a clean, straight line of demarcation is sometimes obtained, often the line is harder to define and there is definite evidence of ink in the cerebral cortex, even though functionally the cats may have acted like the others. Most of our transections were in a limited area close to the rostral limit of the pons. Thus, our information on the exact level of

21. Keller, A. D.: Generalized Atonia and Profound Dysreflexia Following Transection of the Brain Stem Through the Cephalic Pons, J. Neurophysiol. **8**:275-288, 1945.

22. Sherrington, C. S.: On Plastic Tonus and Proprioceptive Reflexes, Quart. J. Exper. Physiol. **2**:109-156, 1909.

23. Liljestrand, G., and Magnus, R.: Ueber die Wirkung des Novokains auf den normalen und den tetanusstarren Skelettmuskel und über die Entstehung der lokalen Muskelstarre beim Wundstarrkrampf, Arch. ges. Physiol. **176**:168-208, 1919.

24. Pollock, L. J., and Davis, L.: Studies in Decerebration: VI. The Effect of Deafferentation upon Decerebrate Rigidity, Am. J. Physiol. **98**:47-49, 1931.

25. Ranson, S. W.: The rôle of the Dorsal Roots in Muscle Tonus, Arch. Neurol. & Psychiat. **19**:201-241, 1928; Rigidity in Deafferented Limbs, J. Comp. Neurol. **52**:341-346, 1931.

transection is insufficient to permit discussion of its effects upon the degree of extensor tonus. A good review of the effect of the exact level of transection upon the extensor tonus and a comparison with the anemic method are made by Ranson and Hinsey.[26] All our experiments were repeated on cats decerebrated by transection, and the results were essentially the same.

Thiopental sodium given intravenously seems to have certain advantages over ether as an anesthetic for decerebration. It is as short-acting as ether, does not require an anesthetist, and does not produce excessive respiratory secretions.

SUMMARY

A "normal" decerebrate cat shows only moderate extensor tonus.

Many factors were found which both stimulate respiration and increase extensor tonus. These factors include suffocation, lack of oxygen, increased carbon dioxide, acidosis, increased body temperature, and certain peripheral stimuli.

The role of body temperature is stressed.

Decerebrate extensor spasms, apparently identical with "tonic fits," are described, along with their methods of production.

Periodic breathing in decerebrate cats is often accompanied by marked variations in extensor tonus.

Deafferentation seems to abolish extensor tonus in the "normal" decrebrate cat but not in the stimulated one.

A paradoxical flexion response is described.

26. Ranson, S. W., and Hinsey, J. C.: Extensor Tonus After Transection of the Brain Stem at Varying Levels, J. Nerv. & Ment. Dis. **70**:584-597, 1929.

Society Transactions

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

Raymond D. Adams, M.D., *President Presiding*

Regular Meeting, April 16, 1953

Auditory Hallucinations in Alcoholism. Dr. Maurice Victor (by invitation), and Dr. Justin M. Hope (by invitation).

This communication is concerned with the clinical features of 70 patients (14 women and 56 men) who presented with auditory hallucinations in an otherwise clear sensorium. All the patients were alcoholics of long standing; 61% had a history of alcoholism present in the immediate family; 63% of the marriages among our patients ended in divorce, and one-third had suffered previous attacks of alcoholic neurologic disease, often differing in nature from one episode to another. The onset of the hallucinations in 85% of the instances was in the period that followed complete cessation of drinking. The longest period of complete abstinence preceding the onset of hallucinations was seven days. The hallucinations were almost always vocal, and in 75% of the cases were derogatory and threatening in nature. Orientation and memory were well preserved during the hallucinatory episode, though insight was usually lacking, and often not regained for days to weeks after the cessation of the hallucinations.

In the majority of cases the hallucinations lasted less than six days. In this group the hallucinations were vivid, and in all instances behavior was appropriate to the hallucinatory content throughout the illness. In sharp contrast was a group of eight patients in whom the hallucinations lasted six weeks to eight months. Four of the eight patients, after an initial period of disturbed behavior, became resigned and unperturbed, although still actively hallucinated. Thus, their behavior became inappropriate, and they voiced persecutory delusions which were not dictated by the hallucinatory content.

Finally, we encountered three patients with a schizophrenic illness who in addition had transient episodes of vivid hallucinations in relation to the excessive use of alcohol.

DISCUSSION

Dr. Robert Fleming: I found this an interesting paper, and the results and conclusions coincide closely with my experience. There are a number of questions. This is a valid way to approach the problem, objectively, statistically, and without preconceived ideas, in contrast to the method in so many psychiatric papers, especially of a psychoanalytical nature, in which that approach does not exist. Of interest to me was the geographical distribution: These cases do not seem to occur in England; they occur on the Continent and here in the United States. Is there some racial distinction between patients with delirium tremens and those with acute hallucinosis? I am impressed by the evidence that the prepsychotic personality does not have much to do with the determination of the symptoms in these cases. At the Boston Psychopathic Hospital we had a Scotchman in his early 40's who had delirium tremens by night and acute hallucinosis by day for about a week.

Dr. Wilfred Bloomberg: I hoped someone would mention the relationship between the functional and the organic in these matters. Work with lysergic acid and Schilder's report on temporal lobe tumors all cut across this line. I don't think we know how alcohol acts, either primarily as a toxin, or secondarily, by its accompanying nutritional deficiency. We do know that as a toxin it seems to act most strongly on the vestibular mechanisms, with ataxia and staggering as an early symptom. When one adds the material developed by Penfield's work on

auras and on formed and unformed hallucinations as a result of stimulation, there arise many questions in relation to the organic or functional localization of hallucinations and the problem of insight or lack of insight.

DR. MORRIS YORSHIS: I come from Methuen, where there was a murder of eight people by an alcoholic with a hallucinosis of the paranoid reaction type. Does it make any difference what a patient drinks?

DR. BRUCE SLOANE: In regard to visual perseveration, Saltzman tested eidetic imagery in hallucinating alcoholics, essentially by the projection of after-images, without finding eidetic tendencies. Thus, it might be said that they did not show demonstrable visual perseveration.

DR. WILFRED BLOOMBERG: I wonder what Dr. Hope is implying when he speaks of the hallucinations occurring after a period of abstinence. Does he believe the abstinence is a contributing cause, or is it incidental? This is not an unimportant question. The problem of whether or not delirium tremens is a withdrawal syndrome and of how to treat it—whether by administration of alcohol or not—appears to me to be reopened by what Dr. Hope has said. I have long believed that delirium tremens, whatever the accompanying vitamin deficiency, is primarily a toxic disorder and that one does not treat intoxication by giving the toxin that caused it. I wonder whether Dr. Hope would comment on this.

DR. JUSTIN M. HOPE: In regard to Dr. Fleming's statement about geographical distribution, we have some data on this point but have not yet analyzed them. Dr. Bloomberg asked about abstinence. That is a very good point, and we are not attempting to dodge the issue. For 53 patients the actual time of the last drink before admission to the hospital was known, and in over half of these the hallucinations had their onset within 48 hours of the beginning of the period of abstinence. There were some whose history indicated that the auditory hallucinations came on while the patient was still drinking. However, the problem of relative abstinence must be considered. For instance, in some of our material on patients with delirium tremens we found that preceding the actual onset of delirium tremens there were episodes of tremulousness, and even hallucinations, which were temporarily relieved by alcohol. Some of these histories assume the following form: The patient, who has been drinking heavily by day, goes to bed. When he wakes up in the morning, he experiences "the jitters", which may be associated with illusions and hallucinations into which he has some insight. One patient saw the animals on the wallpaper in his baby's nursery moving. He took another drink, and this illusion, as well as the tremulousness, disappeared. This pattern of drinking is carried on for a time, when, for various reasons, e.g., lack of money, nausea, or remorse, the patient stops drinking. It is after this period of abstinence, of varying lengths, that the full-blown picture of delirium tremens or auditory hallucinations has its onset. This is not a new observation. Kraepelin observed it. Our material showed that in most instances the onset of auditory hallucinations occurred after a period of abstinence. Abstinence certainly plays a role in the development of all the non-nutritional alcoholic disturbances. Certain hypotheses to explain the role of abstinence in these disorders have come to our minds. However, at the present time we do not have sufficient data on which to arrive at a conclusion regarding the precise manner in which abstinence operates in these conditions. Although abstinence plays some role in delirium tremens, it does not necessarily follow that the administration of alcohol is a satisfactory treatment for delirium tremens once it has developed. We have given some of our patients alcohol while they were in active delirium. The administration of alcohol to these patients did not prevent the delirium from running its usual course.

In connection with the recent tragedy in Methuen, a question was asked regarding the relationship between the type of alcoholic beverage consumed and the type of abnormal behavior resulting therefrom. We have been able to find out in most instances exactly what the patient drank and the amount consumed. I do not believe that one can correlate the type of illness with the kind of alcoholic beverage, i.e., whisky, ale, wine, etc., used. More important to the alcoholic illness were the pattern of drinking and the amount consumed.

Dr. Bloomberg brought up a point regarding the vividness of the hallucinations. Throughout the alcoholic illnesses the vividness of hallucinations is quite apparent, while in some of the

so-called "functional" disorders the hallucinations are less vivid. I do not believe that the content of the hallucinations has much to do with the fundamental physiological disturbance that exists during the illness.

The Triopathy of Diabetics: Diabetic Neuropathies, Malignant Retinitis and Diabetic Nephropathy. Dr. Howard F. Root.

Diabetic neuropathy may manifest itself in many ways. It is certainly not limited to the peripheral nerves but may involve any portion of the nervous system. Not only may peripheral, motor, and sensory nerves be involved, but spinal nerve roots and autonomic pathways concerned with temperature regulation, postural blood pressure adjustment, motor control, and intestinal and bladder function, may be involved. Practically all diabetic patients in whom these diabetic neuropathies develop have had antecedent periods of months' or years' duration of neglected, poorly managed, and poorly controlled diabetes. A common symptom is pain that is characteristically worse at night. Various paresthesias occur.

The retinopathy of diabetes is frequently preceded by neuropathy, but is often not discovered until albuminuria or hypertension has occurred. Nevertheless, retinopathy may be present without either albuminuria or retinopathy for long periods. Separation of the retina may occur, and blindness may often result. In practically all cases retinitis sooner or later is associated with the typical Kimmelstiel-Wilson lesions in the kidneys, or what is called the diabetic nephropathy.

The diabetic nephropathy is ushered in clinically by apparently bland edema; but within a year or so the edema becomes permanent, hypertension develops, retinal lesions advance, and sooner or later uremia results. At autopsy, the typical globular hyaline masses are found in the glomeruli, together with chronic pyelonephritis, nephrosclerosis, and atherosclerosis.

Treatment and prevention are now for the first time demonstrated to rest on the control of the diabetes. A follow-up of 450 young diabetic patients observed for periods of from 10 to 30 years shows clearly that patients whose diabetes is under good control are free of albuminuria and the diabetic triopathy after periods of 20 to 30 years, whereas these lesions are present in 75 to 80% of the patients after 15 years of diabetes if it has not been controlled by careful daily balancing of diet and insulin dose, and urinalyses.

DISCUSSION

Dr. D. Denny-Brown: I am surprised that neuritis involved as many as 55% of chronic diabetics, though it is certainly not rare. Recently we had at the Boston City Hospital an elderly patient with diabetic neuropathy of rather recent origin whose diabetes had been treated carefully for a number of years. She had most meticulously had her urinalysis. She could swear that not once in the last three years had there been any occasion on which the urine had shown the presence of sugar. Yet in the last six months a severe diabetic neuropathy had developed. This story, of course, is not unusual. What was striking was that her blood sugar values were about 180 to 200 mg. per 100 ml. on her regular insulin dosage. It struck me that the problem was like that of combined system disease, in which the patient needs more liver extract than is necessary to restore the blood picture, in order to reverse the neurological signs. I wonder whether adequate treatment of this type of diabetes requires maintenance of blood sugar levels below 100 mg. per 100 ml.

Dr. Samuel H. Epstein: The data I have observed clinically made me feel that there were two groups of patients with neuropathy: those associated with demonstrable signs of arteriosclerosis and those without such clinical signs. Of those two groups, the patients who did well clinically were those that were relatively free of arteriosclerosis. From a prognostic standpoint, one could use that point regardless of what specific treatment the patients were getting. I do not know why these clinical pictures occur. I am intrigued with Dr. Root's suggestion that the same underlying pathology exists in neuropathy as in the other two forms of diabetic triopathy.

Dr. John F. Sullivan: There appear to be two forms diabetic neuropathy will take: the first, a fairly symmetrical, distal neuropathy, generally rather slow to develop, which one would expect to result from some metabolic disturbance, and (2) the other a single or multiple, a

symmetric neuropathy, of rapid development, and possibly related to interference with the blood supply of the nerve. It has impressed me that there is no one common explanation for the neuropathy, but a multiple etiology.

DR. HOWARD F. ROOT: I suppose that in any human being with a chronic disorder there are multiple etiologic factors. However, we seek, and can frequently succeed in distinguishing, the factors of major or primary importance and the factors proved to be of secondary or slight importance. In the patients I have studied such factors as hypertension and vascular disease were eliminated, and we used patients with onset of diabetes early in life and studied the progressive development of the three conditions under discussion. Thus, in a recent case, a youth aged 20 presented a severe neuritis involving the legs. He has had diabetes for several years, with poor control. I predict that he will have retinitis within five years. At that time he will have the evidence of beginning vascular disease, apparent first in the small vessels, the venules, and the arterioles. It is this change in the small vessels that is most specific for diabetes. In fact it is this severe lesion in the arterioles which has been found to be 100 times as common in diabetics as in nondiabetics. The diabetic neuropathy is not confined to the legs, as is well illustrated by the case of a boy of 16 who had diabetic coma. During his recovery both arms became completely paralyzed, and the diagnosis of anterior poliomyelitis was made. However, he made a complete recovery and now, 10 years later, is working hard. The diagnosis had to be altered to diabetic neuropathy. Nocturnal diarrhea, symptoms in the fingers and arms, and other evidences of involvement of the autonomic system occur.

Raymond D. Adams, M.D., *President Presiding*

Regular Meeting May 21, 1953

Carbohydrate Metabolism and Its Regulation in Health and Disease in the Central Nervous System. DR. WARREN S. MCCULLOCH.

What these studies leave to seek will be obvious if we recapitulate them in logical, rather than chronological, order. As to carbohydrate metabolism, brain resembles muscle, including steps from pyruvate through acetyl coenzyme A to the oxidative cycle, CO_2 and H_2O, catching energy in adenosinetriphosphate and storing it in phosphocreatine.

As to carbohydrate regulation, brain has some control surviving destruction of pituitary, vagal, and sympathetic outflows. How brain detects the blood sugar level is still a mystery. Taste raises it; sham feeding lowers it. Interest in movies and games disturbs it. It is less stable in neurotic than in normal subjects. Among these neurotics are some who, for psychological reasons, on eating secrete too much insulin, thus converting sugar to fat and causing a 30% fall in oxygen uptake under otherwise basal conditions. They show so-called hypoglycemic reactions while the falling blood sugar level is still elevated.

In hypoxia and fits the brain consumes many times the normal amount of glucose, is loaded with lactate and pyruvate, which it subsequently oxidizes, but exhausts its phosphocreatine before the concentration of adenosinetriphosphate falls. These changes are insufficient to induce remission in schizophrenia. They may be unnecessary; but only the work on hyperoxic convulsions has a chance of proving it. Though DDT and nitrogen mustards induce cerebellar fits precipitated by CO_2, they cannot be used clinically because they damage the nucleus dentatus. We seek a convulsant to act on hypothalamic structures.

Many schizophrenics with clouded sensorium (Meduna's oneirophrenics) have elevated sugar tolerance curves, perhaps a higher titer of insulin, and are resistant to insulin. The resistance can be transferred to animals by intraperitoneal injection of the patient's blood. They excrete a high-molecular-weight protein, hyperglycemic factor in urine, not found in the normal condition or in other diseases save a few vascular disorders. Though the chemical change precedes clinical symptoms in remission and relapse, it is probably not their cause, for catatonia in man, relieved by intraventricular cholinesterase, shows return toward normal insulin sensitivity; and catatonia produced by a lesion of the brain stem in monkeys is accompanied by insulin resistance, relieved by intraventricular cholinesterase and reprecipitated by intraventricular acetylcholine. This warrants thorough clinical investigation when sufficient quantities of sufficiently pure human cholinesterase become available.

NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY, AND THE NEW YORK NEUROLOGICAL SOCIETY

Joint Meeting, May 12, 1953

Louis Hausman, M.D., *Chairman, Section of Neurology and Psychiatry, Presiding*

New Method for Study of Central Inhibition by Cortical Conditioned Reflexes. DR. FRANK MORRELL (by invitation).

Within a certain range of intensity the suppression of the normal 10-cps. alpha rhythm to a light stimulus is a specific, inborn, unconditioned response. By successively pairing a sound stimulus of low intensity with the light stimulus, the alpha rhythm can be conditioned to respond to a sound stimulus alone. The establishment and differentiation of conditioned reflexes imply the existence of specific excitatory and inhibitory processes, the magnitude and characteristics of which have never been directly observed. We employed two measurements: (1) the graphic demonstration in electroencephalographic tracings of the origin, course, and spread of the induced electrical activity, and (2) determination of the rate of cortical conduction between the occipital and the precentral region.

Three distinct forms of Pavlovian inhibition were established: extinction of conditioned reflex, delayed conditioning, and differential inhibition. The above measurements were made under each of these categories, and our results indicate a significant delay in cortical conduction time whenever the inhibitory process is induced, as demonstrated by the electroencephalogram.

The significant delay in conduction time indicates the presence and measures the degree of the central inhibitory process.

Fatalities in Myasthenia Gravis. DR. LEWIS P. ROWLAND (by invitation).

During the years 1932 to 1952 a total of 156 patients with myasthenia gravis were seen at the Columbia-Presbyterian Medical Center; the known mortality rate was at least 30%. The records of the 35 patients in whom terminal events were observed were reviewed in order to evaluate the factors which might be responsible for the high mortality. On 23 patients postmortem examinations were performed.

Emphasis was placed upon the recognition of premonitory episodes of respiratory failure, provision of adequate anticholinesterase, maintenance of a patent airway, avoidance of sedation for symptoms of hypoxia, early use of the mechanical respirator, tracheotomy, and prevention of pulmonary complications. The frequency of sudden death and the possible respiratory and cardiac mechanisms were also discussed. The development of refractoriness to neostigmine in the terminal phase was observed in several patients, and one patient was unresponsive to neostigmine throughout the course of her disease.

The incidence of thymoma in the autopsy group was 30%, and 66% had lymphorrhages in skeletal muscle. Three patients had lesions which involved destruction of muscle fibers, accompanied by an inflammatory response, and two patients had nonspecific myocarditis. All but three patients examined histologically showed some degree of pulmonary pathology.

DISCUSSION

DR. LAWRENCE H. GAHAGAN: What drugs are recommended in myasthenia gravis?

DR. LEWIS P. ROLAND: Neostigmine must still be named the stand-by; experiments are being tried with new drugs, but I do not think there are any that can completely replace neostigmine.

Cerebral Arteriovenous Aneurysms. DR. MALCOLM B. CARPENTER (by invitation).

Until recent years the diagnosis, localization, and treatment of cerebral arteriovenous aneurysms presented almost insurmountable difficulties. The frequency of these lesions as compared with that of verified brain tumors was found to be about 2%. Available evidence indicated that such malformations occur twice as often in males as in females. The commonest symptoms and signs, in order of frequency, were seizures (usually Jacksonian or focal), spontaneous subarachnoid hemorrhage, intracerebral hemorrhage, psychic and mental disturbances, and headache

(often migrainous in type). The diagnosis on clinical evidence alone is often impossible but can be made on the basis of (1) a history of focal or Jacksonian seizures, (2) spontaneous subarachnoid calcification, (3) the presence of a bruit, and (4) roentgenologic evidence of floccular intracranial hemorrhage. Cerebral angiography offers the best method of establishing the presence of an arteriovenous aneurysm and affords preoperative study of the nature, extent, and precise localization of the lesion. Palliative procedures (viz., irradiation of the lesions, surgical decompression, electrocoagulation, and cartoid ligation) have proved to be unpredictable, and sometimes disastrous, as forms of treatment. Surgical extirpation of the aneurysm is the method of choice, and the risk involved is considered to be less than the risk of leaving the lesion untreated. Recent adjuncts to neurosurgery (i. e., controlled hypotensive states) can be expected to lower the mortality statistics in the future. Three cases of large cerebral arteriovenous aneurysms treated by surgical extirpation of the lesions were presented. Follow-up cerebral arteriography was done to determine the completeness of the removals. Intracerebral hematomas existed in all cases. The progressive nature of the disease was abruptly interrupted, and recovery followed, without additional neurological deficit.

Evaluation of Seizures in the Adult. Dr. Herbert L. Martin and Dr. Fletcher McDowell (by invitation).

Study was made of 245 patients in whom seizures developed after the age of 12, including air encephalography. In 91 patients with generalized seizures, in 48 of whom the seizures began after the age of 35, the neurological status, roentgenogram of the skull, and spinal fluid were normal, and the electroencephalogram did not suggest brain tumor. In none of this group were intracranial mass lesions demonstrable on air encephalography. Seventy-four patients with generalized seizures, in 52 of whom the seizures began after the age of 35, had evidence of focal brain dysfunction on neurological examination, and many had abnormalities in the roentgenogram of the skull or spinal fluid or had an electroencephalogram suggesting neoplasm. Forty-eight of this group of 74 patients had mass lesions, and in 10 cortical atrophy was demonstrable in the air encephalogram.

Of 55 patients over 12 years of age, with focal seizures, examination revealed no abnormality in 13, and of these, 3 had a mass lesion demonstrable by air encephalography. Thirty-nine of this group had evidence of focal brain dysfunction on neurological examination and abnormalities in certain of the ancillary studies. Thirty-three of these had mass lesions, and four had cortical atrophy demonstrable by air encephalography.

Of the total group of 245 patients, 215 had an electroencephalogram recorded. Of the 71 patients with supratentorial mass lesions exclusive of pituitary tumors, 49, or 70%, had electroencephalograms suggestive of neoplasm. Of the 215 electroencephalograms, 52 suggested tumor, and 49 of the patients with these records had tumors. The electroencephalogram, however, is rarely the sole indication of the presence of an intracranial mass lesion.

In short, when in a patient with generalized seizures, beginning before or after the age of 35, the bedside neurological examination fails to reveal evidence of focal brain dysfunction, air encephalography at that moment is not likely to demonstrate a mass lesion. It may, however, reveal cortical atrophy. When subsequent repeated bedside neurological examinaiton first yields evidence of focal brain dysfunction, air encephalography may contribute significantly to localization.

DISCUSSION

Dr. Theodore J. C. von Storch: While I agree wholeheartedly with the principle that has just been expressed, to wit, that neurological examination is extremely valuable, and is often more valuable than a laboratory procedure, I think great caution should be used in evaluating electroencephalographic and pneumographic findings. One has to take into consideration how the examinations are done and how they are recorded.

Dr. Herbert L. Martin: I agree that is important; all these patients had more than adequate, really expert, examinations.

Dr. Louis Hausman: I think Dr. Martin and Dr. McDowell deserve credit in emphasizing what is often forgotten, viz., that there is no substitute for a good neurological examination.

Studies on Headache: Cerebrospinal Fluid Pulsations and Temporal Artery Pulse Waves in Migraine and in Headache Induced by Amyl Nitrite and Histamine; Action of Ergotamine. DR. M MARTIN TUNIS (by invitation), DR. PHILIPPE CARDON (by invitation), and DR. HAROLD G. WOLFF.

An electromanometer connected with the lumbar subarachnoid space through a No. 20 needle was used to amplify cerebrospinal fluid pulsations. The latter were recorded with simultaneous temporal artery pulse waves on a multiple-channel direct writer. The cerebrospinal fluid pulse wave tracings evidenced changes in the contractile state of large intracranial arteries and were compared with simultaneous alterations in caliber of a representative extracranial artery, usually the right superficial temporal.

This method was employed in 20 normotensive patients with normal cerebrospinal fluid pressure to study the vasoconstrictor action of intravenously administered ergotamine tartrate, 0.25 mg. (11 subjects), and the vasodilator effect of amyl nitrite inhalation (6 subjects) and histamine infusion, 0.1 mg. (3 subjects).

During right hemicrania, a large-amplitude right temporal artery pulse wave, with a rounded apex and outward convexity of the diastolic limb, was recorded. Pulse waves of this type (Tunis, M., and Wolff, H. G.: Analysis of Cranial Artery Pulse Waves in Patients with Vascular Headache of the Migraine Type, *Am. J. M. Sc.* **224**:565, 1952) were obtained from the involved artery in numerous subjects during vascular headache. Seven minutes after the intravenous administration of 0.25 mg. of ergotamine tartrates, the pulse-wave amplitude was reduced 100% and the headache intensity was greatly diminished. There was, however, no vasaconstrictor change in the simultaneously recorded cerebrospinal fluid pulse waves. Further, when the patient was headache-free, the cerebrospinal fluid pulse wave tracings were not significantly different from records obtained prior to and shortly after ergotamine therapy for the headache.

During headache induced by amyl nitrite inhalation and histamine infusion, the amplitude of the cerebrospinal fluid pulse wave tracings was increased from 300 to 600%. When headache subsided, the records returned to the control contour in all instances. Changes noted in the simultaneous records of the temporal artery pulse wave were often less marked, of shorter duration, and at times absent during the headache. As well, there was increased steepness of both the systolic and the diastolic limb of the cerebrospinal fluid pulse wave, and the contour of the descending limb was concave downward, with prompt return to the base line during the headache. These findings indicated dilation and distention of intracranial vascular structures and decreased vascular resistance.

Extracranial artery pulse waves from the involved vessel during spontaneous migraine headache also evidenced dilatation and distention. By contrast, however, in all instances, there was an outward convexity of the diastolic limb, which indicated increased vascular resistance, probably related to intramural and perimural edema of the involved vascular structures.

In short, these pulse-wave contour analyses define the differences between headache arising from intracranial arteries (amyl nitrite and histamine) and vascular headache of the migraine type, in which extracranial vessels are the principal source of the head pain.

DISCUSSION

DR. PHILIPPE CARDON: It should be emphasized that this technique is very simple. Anyone who has an electrical device for recording pressure can do it. We used an electromanometer. The usual clinical needle is placed in the subarachnoid space. The apparatus is very easy to set up, and it will be interesting to see what are the possibilities for picking up intracranial pathology. For instance, I should think that in a patient with an arteriovenous aneurysm one would get tracings very much like the amyl nitrite tracings shown by Dr. Tunis.

Water and Electrolyte Metabolism in Migraine. DR. WILLIAM W. SCHOTTSTAEDT (by invitation).

Preliminary studies of renal excretion of water and electrolytes were performed on healthy subjects with and without headache. These studies suggest that there are major alterations in fluid and electrolyte balance in association with headache, characterized by low rates of excretion of water, sodium, potassium, and creatinine prior to headache and high rates of excretion during

the phase of subsidence of headache. When disappearance of headache has not been associated with increased volume of urine, the subject has remained in a headache-prone state, as evidenced by prompt recurrence of headache.

Clinical and Electroencephalographic Studies of Meperidine Addiction. Dr. William D. Voorhees Jr., Dr. James F. Masterson Jr., and Dr. Albert N. Browne-Mayers (by invitation).

The clinical and electroencephalographic records of five men and three women meperidine (Demerol) addicts between 28 and 60 years of age were studied. All were voluntary hospital patients, poorly oriented to psychotherapy, who insisted on being discharged prematurely. Although all the patients stressed physical discomfort as the initial reason for using meperidine, five recognized that emotional factors led to its continued use. Symptoms following withdrawal of meperidine were minimal and apparently unrelated to the reported daily dose or the rapidity of withdrawal, except in the case of a woman who had a series of epileptiform seizures and a man who went into a panic. Intensive directive psychotherapy, a full hospital program of occupational and recreational therapy, and segregation from previously withdrawn addicts combined to minimize symptoms. Personality studies revealed that the patients were proud, tense, rigid, capable people, unable to accept their shortcomings, and striving for recognition. A careful scrutiny of their interpersonal relationships revealed psychopathic features in only three of the patients.

Admission electroencephalograms showed 6- to 7-cps. slow activity in several patients who had normal records four weeks later. One patient showed mild changes in her admission electroencephalogram, but three weeks after withdrawal of the drug a focus in the left anterior temporal lobe appeared. The electroencephalographic findings were variable and appeared to be influenced both by the amounts of meperidine taken and by the sensitivity of the cerebral physiology to the drug.

Nervous System Disorder in Leukemia: Clinicopathologic Study. Dr. Walter Sencer (by invitation).

Although involvement of the central nervous system in leukemia occurs, rarely does the blood dyscrasia simulate a neoplasm, and especially is it uncommon for the disease to present itself early neurologically, and only later with evidence of hematologic pathology. The following case illustrates this point. A man aged 42, was admitted with a cervical root syndrome of 10 weeks' duration, with sudden onset of pain in the right arm, radiating to the first, second, and third fingers. This was followed by pins-and-needles sensations and weakness in the right foot. One week prior to admission blurring of vision and diplopia occurred on his looking to the left. Three days prior to admission he noted that food became lost in his left cheek.

Physical examination on admission was noncontributory except for a hard mass, measuring 3 cm., in the manubrium sterni. Neurological examination of the cranial nerves revealed weakness of the left external rectus with diplopia on left lateral gaze; the corneal reflexes were absent, and there was left facial paresis of peripheral type. The right upper extremity was paretic, and pain occurred with shoulder retraction. The right triceps reflex was absent, and the left knee jerk was decreased. There was hypalgesia over the radial aspect of the right forearm.

On admission a complete blood cell count and urinalysis gave normal results. The sedimentation rates on two occasions were 2 and 4 mm., respectively, in one hour. The heterophile antibody titer was negative. A guaiac test of the stool was negative for occult blood. The spinal fluid was clear; the initial pressure was 140 mm. There was no block. There were 116 white blood cells per cubic millimeter, with 98% lymphocytes and 2% polymorphonuclear leucocytes; the protein was 112 mg. per 100 ml., and the serologic reactions were negative. The EEG was normal. A caloric test revealed impairment of the right vestibular apparatus. Roentgenologic examination of the skull, chest, sternum, and vertebrae revealed no abnormality.

During the last three weeks of his life there was a marked fluctuation of neurological findings, with bilateral involvement pointing to a lesion in the spinal cord and brain stem. Nystagmus and a syndrome referable to the median longitudinal fasciculus developed. Findings on exam-

ination of the sternal marrow and lymph node biopsy were normal during the second week of hospitalization. The patient's course was progressivety downhill, and on the 28th hospital day he became disoriented and hepatomegaly and splenomegaly were noted. The peripheral blood then showed 85,450 white cells, with 82% lymphocytes, 11 prolymphocytes, 3 segmented forms, 2 nonsegmented forms, and 2 eosinophiles, per 100 white cells, and 1 normoblast and 1 erythroblast. The sternal marrow showed 100% myeoloblasts. The patient died five days later. Pathological examination revealed diffuse infiltration of the nervous system, including the brain stem, brachial plexus, and oculomotor nerve. There was tumor formation at the manubrium sterni, which consisted of leukemic cells. This case is interesting in that the acute illness, with multiple and fluctuating neurological findings, pointed to an infectious or demyelinating disease with no laboratory evidence of a blood dyscrasia until a week prior to death.

Etiological Survey of Cases of Aphasia Without Hemiplegia. DR. ARTHUR E. GILLMAN and DR. STEFAN SZANCER (by invitation).

Many patients are admitted to the Psychiatric Division of Bellevue Hospital because of a disturbance in communication. In a relatively large number of instances the difficulty is due to an aphasia not associated with other neurologic signs. This language disturbance apparently creates anxiety in both the patient and the observer, and oftentimes a diagnosis of agitated depression or schizophrenia is entertained. Little information could be found in the literature as to whether aphasia occurring as the only or major sign favored one particular cause over others. The clinical course and etiology in such patients were investigated.

Fifty-eight patients admitted to the neurologic wards of the Bellevue Hospital Psychiatric Division between 1948 and 1952 who presented an aphasic difficulty without other neurologic signs (Group 1, 33 patients) or with minimal associated neurologic findings (Group 2, 25 patients) were investigated.

It was found that a variety of etiologic factors existed and that there was no significant difference between the two groups. Vascular disease was the most probable cause of this condition. It accounted for a little less than half of the total number of patients studied (23 cases). Trauma also was a frequent cause of aphasia (16 patients). Twelve of these did not have signs other than the aphasia on admission. The highest degree and rate of recovery occurred in these patients. Degenerative disease (presenile dementia) was next in frequency (11 patients). Here no improvement was noted. The percentage of neoplasm was unexpectedly small (3 patients, or approximately 5% of the total). All the patients with neoplasm were in Group 1, that is, associated with some other, less apparent neurologic manifestation.

It was emphasized that the psychogenic factors secondary to language disorders are very common and often can obscure the underlying basic neural dysfunction.

Abstracts from Current Literature

Physiology and Biochemistry

Associated Movements Between Limb and Respiratory Muscles as a Sequel to Brachial Plexus Birth Injury. P. K. Robinson, Bull. Johns Hopkins Hosp. **89**:21 (July) 1951.

Simultaneous contraction of muscles which do not normally act together, although supplied by the same nerve, has long been observed to follow injury of that nerve. In an effort to observe the frequency of this associated activity, all adults whose records were available through the files of a general hospital and who had had damage to the brachial plexus at birth were examined for evidence of such movements. The results in a series of eight unselected persons, examined at intervals of from 9 to 23 years after injury, are the subject of this report.

Associated movements of muscles of respiration and of partially paralyzed limb muscles, as shown by contraction of the latter during deep inspiration, were found in six of the patients. To demonstrate that such abnormal activity might occur as a result of damage either to the phrenic nerve or to the nerve supply to the accessory respiratory muscles, the author studied the effect of use of the limb muscles on those of respiration. Fluoroscopic study of five of the six patients demonstrated diaphragmatic contractions in three when the elbow was flexed. In one patient contraction of the limb muscles produced associated activity in one of the superficially placed accessory respiratory muscles.

According to Robinson, an explanation of the abnormal simultaneous activity of the limb and the respiratory muscles is possible on a structural basis. The respiratory muscles in question are the diaphragm and the accessory muscles of respiration, namely, the trapezius, sternocleidomastoid, pectoralis, latissimus dorsi, and scalenus muscles. All the accessory group except the first two are supplied by nerves having their origin in the fifth to eighth cervical and first thoracic roots, which form the brachial plexus and supply the limb muscles also. The part of the diaphragm which arises from the septum transversum is innervated by the phrenic nerve, which itself receives a rootlet from the fifth cervical root. Injury to the fifth root proximal to the origin of this rootlet may permit the central regenerating fibers, which originally went to the arm, to descend into the phrenic nerve and innervate the diaphragm; thereby contraction of the limb muscles will cause the diaphragm to descend. Similiarly, contraction of accessory respiratory muscles may occur during limb movements when the plexus itself is damaged at a point where innervating fibers run close together. The converse, namely, contraction of arm muscles during inspiration, may be produced by injury at either of the sites mentioned. Robinson believes that this phenomenon is much more frequent than has hitherto been thought.

Alpers, Philadelphia.

The Site of Excitation in the Nerve Trunk of the Frog. W. A. H. Rushton, J. Physiol. **109**:314, 1949.

Space Distribution of Excitability in the Frog's Sciatic Nerve Stimulated by Slot Electrodes. C. Rashbass and W. A. H. Rushton, ibid. **109**:327, 1949.

Space Distribution of Excitability in the Frog's Sciatic Nerve Stimulated by Polar Electrodes. C. Rashbass and W. A. H. Rushton, ibid. **109**:343, 1949.

Relationship Between the Slot Excitability and the Excitability Due to a Single Pole. C. Rashbass, ibid. **109**:354, 1949.

In this series of four papers, which are so closely related that they must be considered as a whole, the authors present detailed observations regarding the distribution of excitability along the sciatic nerve of the frog at and near the stimulating electrodes. Their observations lead to the postulation of certain new concepts regarding the spatial distribution of the

excitability which explain satisfactorily their own precise measurements and which may be used to clarify previous observations and interpretations of excitability. Although these previous observations have been explained by means of the classic cable theory of nerve excitation, the concepts of excitability in the present studies are incompatible with the cable theory.

The first paper deals with a new, significant observation, which forms an important basis for the subsequent studies of excitability. A pair of electrodes set very close together, e. g., 1 mm. apart, was used to stimulate the nerve. Because of the method used to obtain this small electrode separation, the electrodes are referred to as slot electrodes. On stimulating with such a pair of electrodes, it was found that the impulse did not originate at the cathode, the correctness of this observation being demonstrated by two independent methods.

The first method verifies the assumption that excitability (equal to the reciprocal of threshold) is greatest about 3 mm. from the cathode. From this assumption, it would follow that if two pairs of slot electrodes 6 mm. apart were arranged with their cathodes toward each other, the maximum excitability due to each would coincide in space. Thus, the observed latent period between stimulus and the beginning of the action potential recorded at a distance away would be the same after each individual stimulus. This is found to be so. From the assumption just stated, it would also follow that, since each cathode would excite at the same point, the effects of the two stimuli would be additive when they are made to coincide in time. When the threshold for stimulation is determined (the action potential is used as the response) by varying the strength of each stimulus, it is found that their effects are indeed additive when the electrodes are separated by the proper distance which gives an identical latent period for each stimulus. If the strength of one stimulus (X) is plotted against the strength of the other (Y) with cathodes facing each other, a straight line is obtained, inclined at a 45 degree angle to each axis. Thus, it crosses the X axis when $Y = 0$, and it crosses the Y axis when $X = 0$. By the reversal of one or both pairs of stimulating electrodes, other relationships are obtained, predictable as well on the idea that the two effects are additive.

That the effects of the two stimuli are additive in all proportions is further borne out by similar threshold measurements with the slots separated by various distances other than the distance critical for maximum summation. In these determinations, the points of maximum excitability do not coincide, and a plot of X against Y will no longer be a straight line, an indication of less effective summation. Each line relating Y to X will, of course, cross the X axis at the same point, since here $Y = 0$. The slope of this line where it crosses the X axis depends on the separation of slots and is related to excitability at the existing excitation site. This determination forms a method for measuring the spatial spread of excitability, which is described in detail in the second paper of the series.

The second method used to demonstrate the origin of the impulse at about 3 mm. from the cathode of a pair of slot electrodes is based on the recording of action potentials at and adjacent to the cathode. This method enables the localization of the action potential, and therefore the determination of the direction of flow of current during activity, without interference from the stimulus artifact. It was found that the current passed in through the membrane, indicating activity, at the same time at distances of 1, 2, 3, and 4 mm. from the center of the stimulating slot. In the neighboring regions, i. e., at 0, 5, and 6 mm. the current passes outward. Thus it is seen that excitation occurs simultaneously along a stretch of nerve extending 3 mm. from the cathode.

The second paper describes the detailed measurement of the slot excitability curve, that is, the spatial distribution of excitability in nerve stimulated by slot electrodes. The curve is then used to predict other results of excitability measurements.

The slot excitability curve is obtained by two methods. The first was indicated in the first paper and is mentioned in the abstract of that article. The excitability of the nerve stimulated through one slot electrode (Y) may be determined by measuring the effect of the stimulus when its strength is rather small, as compared with that of another slot (X), whose strength is very close to threshold. By varying the distance of Y from X, the excitability of the nerve at different distances may be plotted. The second method is based on symmetry of stimulation of the two slots. Threshold is found for various separations of the slots, the same point on the nerve, halfway between the electrodes, being always kept. One may add the ordinates

of the two excitability curves and determine the point of maximum excitability. A quicker method is described for accomplishing this. One may predict from the slot excitability curve found by the first method the threshold for symmetric stimulation (the second method) with any separation of the slots, and also the point at which stimulation will arise. The experimental results from this simpler method of symmetric stimulation confirm the predictions up to a slot separation of 10 mm. Latency measurements are also made in these experiments to indicate the site of excitation.

The slot excitability curve may be described as follows: From the origin at the cathode, excitability increases to a rounded maximum at a distance of about 3 or 4 mm., and then gradually decreases to zero at a distance of about 15 mm. From the slot excitability curve, predictions are made for the spatial distribution of excitability and also for latency for any separation of two slots and for any strengths of stimuli delivered by the slots. These predictions from general considerations are verified by experiment.

The results are discussed in relation to two prime assumptions, both of which are found to apply to the narrow conditions of the experiments. However, they are not universally applicable, as seen from results of previous experiments. The first assumption states that two or more potentials at some one point in the nerve structure (e. g., membrane depolarization at that point) are additive. The authors refer to this as the "superposition theorem." The second assumption states that in order for excitation to occur at a given point the membrane depolarization at that point must attain a critical threshold value; i.e., the stimulating current leaving the nerve at that point must attain a fixed value.

Previous work has shown that the superposition theorem does not apply around threshold conditions. In these experiments it does. Explanations for the validity of the theory are discussed. In these experiments, the authors use two stimuli of the same time course but separated in space so that each has a different spatial distribution. By this means it was possible to obtain a fixed current at a single excitation site, and the superposition theory applies.

In the third paper, the authors apply successfully the results and conclusions of the two previous papers to a more general consideration of space distribution of excitability. According to the classic theory of nerve excitation, based upon the cable structure, excitation always occurs at the cathode, no matter what the separation of the electrodes. With the electrodes close together more current is needed to excite, owing to the fact that anodal depression tends to neutralize cathode stimulation. It also follows from classic theory that excitability decreases exponentially with distance in the extrapolar region. It was shown in the previous papers that neither conclusion is true. Excitability observations will now be interpreted in the light of the present results.

Experimental approach is made through the evaluation and comparison of thresholds obtained with bipolar and with tripolar stimulation. According to the cable theory and its deduction that excitation arises at the cathode, and assuming the validity of the superposition theorem, the thresholds will be the same. But they are not always the same, since it is seen that excitation does not arise exactly at the cathode. The divergence gives information regarding the usual case of bipolar stimulation and is studied in the following manner.

A nerve is arranged to be stimulated with either two or three electrodes. In the case of tripolar stimulations the center electrode is the cathode and each end one is an anode. In the case of bipolar stimulation either one or the other of the anodes is not used. A technique is described for obtaining a constant potential gradient between electrodes and zero gradient in extrapolar regions; and an abrupt change of gradient, which is well localized at the electrode. The nerve and cathode were always fixed, and each of the other two electrodes are movable.

The results of excitability measurements are expressed as a graph relating threshold to electrode separation. The bipolar curve is exponential, which follows from the cable theory. But the tripolar curve is not identical and throughout its course shows a lower excitability. This is contrary to the cable theory. Furthermore, latent period measurements in the bipolar experiments show that excitation does not arise always at the cathode. As shown in the previous papers, with small electrode separation excitation may arise as much as 3 mm. away from the cathode.

In order to explain these results, the distribution around a single electrode is determined. (A single electrode is far enough removed from any other to be uninfluenced by it.) It is found

that the single-pole excitability curve shows maximum excitability at the cathode; excitability falls off symmetrically on either side of the cathode. It is shown with the aid of the superposition theory that the single-pole excitability curve can be derived from the slot excitability curve, for the differential of the former is equal to minus the latter. It is further shown that in symmetric tripolar stimulation, the excitation site is always at the cathode.

By the use of the superposition theory, one may obtain by means of the tripolar excitability curve (which is equal to the single-pole excitability curve when inverted) both the bipolar excitability curve and the latent period curve. Thus, the deviations from the cable theory can be predicted.

Asymmetric tripolar stimulation was used by stimulating with different currents between each anode and the central cathode. The experimental results on threshold measurements agree very satisfactorily with theoretical results predicted from the tripolar excitability curve.

Although the results and concepts presented in these papers cannot be explained on the basis of the cable theory, the authors make no attempt to discuss the possible structure of the nerve trunk necessary to explain their theory, which they believe to be applicable to any excitability distribution. They conclude by generalizing their theory to show how excitability at every point on a uniform nerve may be predicted when the distribution of the stimulus is known.

In the fourth, and last, paper of this series C. Rashbass presents experimental evidence to show that the distribution of excitability around a slot is related to the distribution of excitability around a single pole. In the previous paper this relationship was deduced mathematically from the superposition theorem. In the present paper both curves were determined on the same nerve, using the same apparatus. The experimental results bear out the theoretical consideration, that the differential of the single-pole excitability is equal to minus the slot excitability curve.

WAGMAN, Philadelphia.

ASTASIA-OPTICOKINETIC NYSTAGMUS TEST IN CASES OF CRANIOCEREBRAL TRAUMA. B. ROCHAIX, Riv. oto-neuro-oftal. **26**:391, 1951.

This test consists of having the patient watch a revolving striped drum. In a normal subject nystagmus appears, with a slow component in the direction of the drum and a quick one in the opposite direction. No subjective dizziness or other type of discomfort accompanies the nystagmus. There is no tendency to veer in any direction. The following syndrome is considered abnormal; (1) absence of opticokinetic nystagmus; (2) irregularity of this induced nystagmus; (3) veering of the trunk in the direction opposite that of the movement of the drum, and (4) spontaneous dizziness. The abnormal findings disappear when the movement of the drum is stopped. They are significant only if they can be repeated with the same movement of the drum. The test was positive in 37.5% of 240 patients with head injury in the late stages. One or more of these abnormal findings are usually found with a particular movement of the drum. The incidence of abnormal findings bore no relation to the time after the injury (up to six months). Age played some role, the positive findings being somewhat more frequent in older patients. This syndrome may disappear; it is present at times even when the patient is subjectively entirely better. On rare occasions negative findings become positive again as the patient is followed. This is usually due to superimposed disorders, such as alcoholism or cerebral arteriosclerosis. Sixteen patients were followed over a long period. The average duration was eight months; in the most stubborn case the duration was three years. In all cases the subjective posttraumatic syndrome had cleared up when the astasia-opticokinetic nystagmus test became normal. There was no relation of the incidence of positive findings to the type of head injury. When patients with cervical spine injury were excluded, 73% of the patients with positive findings and 25.3% with negative findings complained of vertigo. Eighty per cent of the patients with negative findings complained of vertigo during the opticokinetic nystagmus: this was true in only 56.9% of the patients with positive findings. Headache was noted in 82% of the patients with positive tests and in 59.3% of the patients with negative tests. A positive astasia-opticokinetic nystagmus test was the most frequent finding in head injury in the author's experience; he considers it a reliable additional objective test for organic injury to the brain. Nine per cent of the patients with a positive test and 51.3% with a negative test showed no other evidence of organic disease of the nervous system.

N. SAVITSKY, New York.

Effect of Hypophysectomy on Intraocular Pressure in Normal Rabbits and in Rabbits Subjected to Hydration. V. Cima, Riv. oto-neuro-oftal. **27**:497 (Nov.-Dec.) 1952.

In 1921 Imre noted intraocular hypotension in patients with acromegaly and other tumors of the hypophysis. Cima hypophysectomized 64 rabbits. In the 37 which survived intraocular tension was measured by the method of Schiøtz for periods up to 28 days. The hypophysectomy caused a decrease in intraocular pressure in most of the rabbits. In normal animals, hydration (administration of 40 cc. per kilogram of distilled water by ingestion—technique of Schmerl and Steinberg) caused an increase in intraocular tension of 15 to 25 mm. Hg. Such an increase in intraocular tension following hydration did not take place after hypophysectomy. The studies indicate the existence of physiologic relationship between the hypophysis and intraocular tension.

N. Savitsky, New York.

Neuropathology

Histological Studies of Muscle Tissue in Neuro-Muscular Diseases. W. R. Kirschbaum, J. Neuropath. & Exper. Neurol. **2**:373 (Oct.) 1952.

Kirschbaum undertook these histologic examinations to determine whether changes occur in certain diseases of the striated muscle tissue which are characteristic enough to be of diagnostic and prognostic significance.

This study is based on biopsy and necropsy material of man and several species of animals. From his findings the author concludes that changes occur in denervated muscles of animals and man which are of diagnostic and prognostic value in connection with all the clinical findings. It is possible to obtain, by biopsy, a reliable answer as to the state of the muscle and its eventual reinnervation.

The significant changes in the muscle tissue are not pathognomonic for certain neuromuscular diseases. They display a general reaction pattern, in which the vascular pattern and the reticuloendothelial system participate. In this pattern two reactions can be separated: (*a*) the purely atrophic denervation phenomena, with preservation of the sarcolemmal membrane, and (*b*) the degenerative phenomena, due to local or general disturbances of the sarcolemmal and endomysial lining. The basic reactions of the muscle fiber are frequently mixed owing to additional circulatory, vascular, and metabolic changes, a condition accounting for the variations and transitions of the histologic pictures.

Alpers, Philadelphia.

Clinicopathological Studies in Epilepsy. Octavio Perez Velasco, Arq. neuro-psiquiatria **8**:301 (Dec.) 1950.

Eighty-two patients with essential epilepsy were studied anatomically, the ages ranging from 8 to 60 years, with 80% of patients from 10 to 40 years of age. All the patients were chronic, and many of them had dementia; no correlation was noted in the anatomic findings, frequency of attacks, duration of the illness, or age of the patient. In all patients there was an evident asymmetry of the brain, involving especially the rhinencephalon. The cerebellum was found to be smaller on the side of the smaller cerebral hemisphere. The thalami, temporal lobes, and white matter of the frontal lobes were all asymmetrical, these structures being smaller on the side on which the cornu ammonis was more severely sclerosed. Sclerosis of the cornu ammonis was observed in 92% of the cases, being usually more marked on one side than on the other. In the cornu ammonis there were fewer ganglion cells, and gliosis was present. In other parts of the brain increase in glial tissue was not noted. The mamillary body was always smaller on the side of the smaller cerebral hemisphere. In 19% of the patients the septum pellucidum was dilated. Cirsoid aneurysms were often noted over the hemispheres in the frontoparietal region. The author believes that these changes are due to a developmental defect of the brain.

N. Savitsky, New York.

Psychiatry and Psychopathology

ORBITOFRONTAL LOBOTOMY. J. R. GREEN, R. E. H. DUISBERG, and W. B. MCGRATH, J. Neurosurg. **9**:579 (Nov.) 1952.

The undesirable effects of the standard frontal lobotomy are well known. They include changes of personality in respect to loss of social consciousness, ambition, imagination, and foresight and a fairly low percentage of postoperative complications, including hemorrhage, infection, epilepsy, and urinary incontinence .

This investigation concerns the results of selective frontal lobotomy of the orbitofrontal area in 55 chronically institutionalized psychotic patients, who had been committed to a state psychiatric hospital for an average of eight years. The authors decided upon orbitofrontal lobotomy instead of the standard procedure for the following reasons: 1. They wished to reduce the degree of blunting of the personality and the complications that follow the standard frontal lobotomy. 2. The unconfirmed reports of Hopstalter and associates in 1945 were encouraging. 3. There is anatomic and physiologic evidence of concentration of frontothalamic projections in the orbitofrontal areas.

Twenty-nine of the 55 patients have been discharged from the hospital. Eight are entirely independent; 11 are partially self-supporting, and 10 remain under supervision at home. Twenty-five patients have remained in the hospital, with 17 showing improvement enough for transfer to open wards and part-time work. One patient died, but death was not considered an operative fatality.

Convulsive seizures following lobotomy have occurred in three patients. There were no instances of postoperative hemorrhage or of persistent urinary incontinence. Relatively little correlation of clinical symptoms with electroencephalographic and pneumoencephalographic studies was observed.

The authors feel that orbitofrontal lobotomy was relatively effective in this series of patients in normalizing emotional responsiveness, without the production of the undesirable blunting of personality or the usual incidence of postoperative complications that accompanies less selective procedures of this nature.

ALPERS, Philadelphia.

LIFE SITUATIONS, EMOTIONS, AND NASAL DISEASE: EVIDENCE ON SUMMATIVE EFFECTS EXHIBITED IN PATIENTS WITH "HAY FEVER." T. H. HOLMES, T. TREUTING, and H. G. WOLFF, Psychosom. Med. **13**:71 (March-April) 1951.

Holmes, Treuting, and Wolff performed this study under uniform conditions in the New York Hospital. Observations on 31 subjects, whose ages varied from 13 to 60, were made from one to six times a week for periods lasting from one week to two years. Of the subjects, 20 had a history of seasonal "hay fever" (August and September) and positive cutaneous or ophthalmic tests for ragweed sensitivity.

The nasal mucous membranes were observed directly through a nasal speculum, and the degree of swelling, amount of secretion, and changes in blood flow were measured in accordance with well-defined standards. Simultaneously, information concerning the subject's life situations, emotional reactions, attitudes, and mood was obtained. Data on daily variations in atmospheric pollen concentration during the hay-fever season were obtained from counts made at the Roosevelt Hospital.

Both before and during the hay-fever season all subjects were observed for approximately one hour from 1 to 20 times each in a room containing a known concentration of mixed ragweed pollen circulated in the air by an electric fan.

In this well-planned study the functional state of the nasal mucous membranes and the reactions to mixed ragweed pollen were investigated. Observations were made on 11 subjects who had nonhyperfunctioning nasal mucous membrane on exposure to mixed ragweed pollen. Two subjects with hyperfunctioning nasal mucous membrane were subjected to mixed ragweed pollen. The relation of the life situation engendering conflict and the relation of nasal hyper-

function to the genesis of experimental hay fever were studied. Finally, neural mechanisms involved in the production of nasal hyperfuntion associated with life situations engendering conflict were studied.

In summary, Holmes, Treuting, and Wolff report that exposure of both "non-sensitive" and "sensitive" subjects to mixed ragweed pollen provoked a response in the nose of mucosal hyperfunction characterized by hyperemia, hypersecretion, and swelling.

The onset and intensity of hay-fever symptoms and the extent of the reaction of the mucous membrane were directly related to the magnitude of the nasal hyperfunction existing at the time of exposure to pollen.

The intensely hyperfunctioning nasal mucous membranes, in contrast to those exhibiting average or mild hyperfunction, reacted promptly to assault by pollen with prompt, intense, and prolonged symptoms and pathologic tissue change characterized by pitting edema and opalescent pallor.

A life situation engendering conflict and anxiety and a response of nasal hyperfunction enhances (1) the intensity of the symptoms of rhinitis and the magnitude of the mucous membrane response already present in "sensitive" subjects, or (2) the response of the nasal tissue to an additional assault by pollen.

Parasympathetic neural impulses to the nose appear to be responsible for the production of the nasal hyperfunction which accompanies the subject's reaction to a situation of conflict.

The character of the hay-fever syndrome appears to depend not only on the intensity of the nasal hyperfunction produced by the exposure of "sensitive" persons to pollen, but on the magnitude and duration of the hyperemia, hypersecretion, and swelling in the nasal chambers produced by other threats and assaults to bodily integrity. Of major importance among these etiologic factors is a life setting engendering conflict and anxiety.

The concept of the summative effects of nasal hyperfunction engendered concomitantly by two or more threats or assaults to bodily integrity appears to afford a basis for a broader understanding of the natural history of the hay-fever syndrome, as well as other common acute and chronic disorders of the nasal spaces.

GUTTMAN, Wilkes-Barre, Pa.

VISUAL HALLUCINATION OF THE SELF. JEAN LHERMITTE, Brit. M. J. **1**:432 (March 3) 1951.

Autoscopy, or visual hallucination of the self, is a sensation experienced by a patient in which he sees his body image as reflected in a mirror. The phenomenon may appear suddenly while the patient is wide awake, but oftener it appears when he is lost in thought or is drowsy. Oddly, the state of authentic dreams is only rarely the source of the hallucination. The image seen is clear but not vivid in color. It fades away when the subject tries to approach it. Sometimes it appears as though it were projected on a screen, whereas at other times it appears to have a jelly-like consistency. Another strange feature of the phenomenon is the feeling of the subject that he is connected to the image by spiritual and material links. Often at the source of the phenomenon is anxiety. Visual hallucination of the self has also been known to be associated with various diseases of the central nervous system, such as epilepsy, dementia paralytica, encephalitis, the encephalosis of schizophrenia, focal lesions of the brain, and post-traumatic disorders.

Lhermitte points out that investigations relating to the body image indicate that "we possess at the boundary of our consciousness the notion of our physical personality—an idea, in the Greek philosophers' sense, of our body. If this image can disappear or be distorted through various diseases of the nervous system, it can also release itself partly from its material frame to become a hallucination—in other words, a perception without object."

ECHOLS, New Orleans.

Meninges and Blood Vessels

CRANIAL ARTERITIS. D. F. KIMMERLING, Ann. Int. Med. **36**:1520 (June) 1952.

A case of cranial arteritis occurring in a woman aged 69 is presented, with a description of the funduscopic changes. This disease usually affects other branches of the common carotid artery as well as the temporal. No etiologic factor has yet been demonstrated. The pathology

of cranial arteritis is that of a granulomatous lesion with cellular infiltration of round cells and fibroblasts in all coats of the artery and numerous giant cells in the media. Thrombosis due to intimal involvement is frequent, but aneurysm formation does not occur.

Clinically, all reported cases have been characterized by headache, although usually it is not the initial complaint. Pain later becomes centered over the affected vessels and is frequently associated with hyperesthesia of the scalp. The headache is constant and severe, frequently unrelieved by opiates. Pain in the temporomandibular joint is often present on mastication, and may be the first painful symptom. Fever is usually low-grade. Anorexia, malaise, loss of weight, weakness, night sweats, and fleeting joint pains are often encountered. Nausea, vomiting, and dizziness may occur.

Ocular symptoms are present in approximately one-half the cases of temporal arteritis and vary from scotomata, photophobia, blurring of vision, diplopia, and constriction of visual fields to complete amaurosis. There is no typical ophthalmoscopic picture, but either an occlusion of the central retinal artery or diffusely scattered arterial lesions with hemorrhages and exudates are seen.

Major physical findings are limited to the head and neck. One or both of the temporal arteries are always prominent, indurated, tortuous, and tender. If the vessels are thrombosed, pulsations disappear, and nodules may be palpated. In the author's case the involved areas were proved to be warmer than elsewhere. This patient had no adenopathy, but enlarged cervical, preauricular, and postauricular glands have often been found. Hypertension has not been found to be out of proportion to the age group of the afflicted patient. The principal laboratory findings are leucocytosis, moderate anemia, and elevation of the sedimentation rate, in this case to 98 mm. (Westergren).

Treatment has varied from resection of a segment of the affected temporal artery to injection of procaine hydrochloride about the inflamed area and the use of x-ray therapy to the temporal region. Chemotherapeutic agents have been used, but their effects were questionable.

Kimmerling and Mordin used vasodilating drugs and believe that these agents should be tried. Their patient's headache was relieved two weeks after admission, and pulsations in the temporal artery returned one week later. Improvement in vision was noted on the sixth day of hospitalization, and was continued during the remaining period of hospitalization in both visual and retinal findings.

The prognosis of cranial arteritis appears to be good, and the disease is believed to be self-limited. The duration is variable, ranging from 6 to 24 months. Lasting diminution in vision and, in many cases, permanent blindness constitute a serious outlook for ocular complications.

ALPERS, Philadelphia.

BRAIN TUMORS SIMULATING MENINGITIS. I. A. BROWN and W. T. PEYTON, J. Neurosurg. **8**:459 (Sept.) 1951.

It is known that meningeal irritation with associated meningitis may be caused by numerous agents. It is well for the clinician to be aware that meningitis may develop during the course of a brain tumor.

Cerebral tumors as a rule produce no change in the cell count of the cerebrospinal fluid. When, however, intracranial tumor is associated with large numbers of cells in the cerebrospinal fluid, necrosis of the tumor or myelin destruction in the perineoplastic area is assumed to be the cause.

An analysis of a report by Henderson and de Gutiérez-Mahoney on the cerebrospinal fluid in brain tumors shows the greater frequency of spinal fluid pleocytosis in glioblastoma multiforme. Of 43 cases of glioblastoma multiforme, 13 pleocytosis, with a count ranging from 14 to 70 cells, of which large numbers were polymorphonuclear. In all such cases the ventricular walls were infiltrated with tumor. Metastatic tumors were not infrequently accompanied by cerebrospinal fluid pleocytosis, whereas other types of cerebral tumors were associated with an increase of only one or two cells over the normal values.

Brown and Peyton report three cases of brain tumor which presented itself as meningitis. In the first a dermoid cyst involved the inferior portion of each frontal lobe, with a long history of sinusitis. There was onset of acute illness upon blowing the nose, with severe meningeal reaction, fever, leucocytosis, and pleocytosis. Partial removal and evacuation of an intracerebral

cyst was followed by recovery. In the second case the patient was admitted in a semicomatose condition, with pronounced pleocytosis and signs suggestive of meningitis. The abnormal course of the illness prompted further investigation, which revealed brain tumor involving the frontal lobes. The patient remained comatose after partial removal of the tumor, which proved to be a glioblastoma multiforme, and died one week later. The third case was one of cerebral varix involving the third ventricle, producing clinical and laboratory signs of meningitis. Because of the clinical findings and the presence of organisms in the spinal fluid, the patient was treated with large doses of penicillin. Later, however, bilateral choked disk developed, with retinal hemorrhages. Ventriculographic study showed bilaterally symmetrical hydrocephalus. Two days after this procedure the patient suddenly passed into a semicomatose condition, which terminated fatally.

The authors point out that intracranial neoplasms should be accorded an important place in the etiology of meningitis. Any meningitis with an abnormal course should be viewed with suspicion and further studies should to determine the etiology should be made.

ALPERS, Philadelphia.

VASCULAR SPASM. G. W. PICKERING, Lancet **2**:845 (Nov. 10) 1951.

Pickering discusses vascular spasm as it is reported to occur in various organs of the body and states that the idea of severe and localized contraction of an artery, i. e., vascular spasm, occurring in the absence of a recognizable stimulus is entertained too freely and uncritically in current thought and writing. He differentiates vasoconstriction and vascular spasm, the former being a contraction under the natural circumstances of bodily function and the latter a vascular contraction sufficient to occlude a vessel and produce symptoms of ischemia from the territory it supplies.

He points out several misconceptions of the role of vascular spasm. The first is that when a subject with occlusive arterial disease of the limbs, such as thromboangiitis obliterans or atheroma, is exposed in a cold room, the temperature of the digits will fall almost to room temperature. If sympathetic vasoconstrictor tone is abolished by warming the body or by spinal anesthesia, the skin temperature rises to a level higher than that of the room. The concept that this is a measure of the degree of vascular spasm present is nonsense, says the author, since a normal person similarly exposed shows a similar reaction, with even a faster and larger rise in skin temperature, so that, according to the common idea, the degree of spasm is much greater in the normal person than in the patient with arterial disease. Likewise, experimental studies of occlusion of the femoral artery have shown that the symptoms may be identical to those of so-called spasm; that is, the blood flow drops immediately to zero and then recovers, returning in a few minutes to as high a value as it had before. This restoration of blood flow occurs through the collateral supply down the back of the thigh, though the exact mechanism by which these vessels expand is unknown. He reports that in some instances an embolus may also give an immediate and severe reduction in blood flow to the limb, but the circulation soon returns.

In the severer cases of Raynaud's disease the digital arteries are always abnormal, displaying evidence of recent and old thrombi in all stages of organization and recanalization. The progress of the disease is due to the laying down of fresh thrombi in the digital vessels. Excision of the sympathetic nerves to the involved limb produces precisely that degree of improvement that might be expected if normal sympathetic activity were removed from a limb. In Raynaud's disease due to cervical rib the condition, again, is due not to pressure on the sympathetic nerves in the brachial plexus but, rather, to injury of the subclavian artery, thrombi being deposited in its walls and then detached, to block the peripheral arteries.

In discussing spasm in retinal arteries, Pickering states that in the patients he has seen the cause has turned out to be embolic. He adds that arteries do not contract violently as a mere whim, but contract only in response to a definite stimulus. The narrowing of the caliber of the retinal arteries in essential hypertension is constant and due to organic vascular change, not spasm.

As to spasm in cerebral arteries, the author states that in recent years the idea of cerebral arterial spasm has been freely entertained in the explanation of attacks of transient paralysis in patients with essential hypertension. This concept he finds particularly difficult to accept.

In the first place, these attacks usually occur without any precipitating factor. Consciousness is not lost. If the transient hemiplegia, hemianopsia, or aphasia is due to ischemia consequent on spasm of the appropriate artery, the other cerebral arteries must remain fully patent. Arteries do not contract without a stimulus, and any evidence as to the nature of this stimulus, which must be quite local, is strikingly absent. Second, physiological experiment has left no doubt that the cerebral arteries are among the least reactive in the body. They are thin-walled, and their media contains little muscle.

The idea of localized cerebral arterial spasm, therefore, seemed to violate the cardinal principles of vascular behavior. Similar attacks of transient paralysis occurred in patients with mitral stenosis and auricular fibrillation. These attacks may, with reasonable probability, be attributed to sudden blocking of a cerebral artery by an embolus. If, in embolism, sudden arterial occlusion may lead to focal symptoms of cerebral ischemia that are quickly reversible, it is probable that the precisely similar attacks in hypertension are likewise due to organic occlusion of a cerebral artery.

That there are free anastomoses between the cerebral arteries at all levels is now known. If we can assume that what happens in the leg also happens in the brain, it would seem that when an artery is blocked, the blood flow in the territory it serves will fall to zero, later to return to normal.

How the arteries become obstructed suddenly in hypertension is unknown. Three lesions seem possible—thrombosis, hemorrhage into the wall, and sudden expansion of the wall, giving the histological lesion that is known as arteriolar necrosis. We are familiar with the occurrence of all these lesions in the arteries and arterioles in hypertension. That a sudden and transient focal loss of cerebral function may be due to organic occlusion of a cerebral artery is, therefore, in conformity with the known facts of vascular behavior, whereas the concept of cerebral vascular spasm is not.

MADOW, Philadelphia.

SUBDURAL EFFUSIONS IN PURULENT MENINGITIS. H. EVERLEY JONES, Lancet **1**:891 (May 3) 1952.

Jones reports on 6 infants with subdural collections of fluid from a total of 12 with purulent meningitis treated over a nine-month period. From three of the six infants the Meningococcus was recovered; from one, Hemophilus influenzae, and in two no organism was found.

In most patients the subdural fluid is found during the first 14 days of life, but may be found up to the age of 62 days. A continued fever associated with restless anxiety and tense fontanels after three to four days of adequate therapy is an indication for needling the subdural space. The amount of fluid obtained ranges from a few drops to over 50 cc. at a time and the accumulation may be found on one or both sides. The fluid is nearly always yellow, and the protein content in the early stages is considerably higher than that of cerebrospinal fluid withdrawn at the same time. Usually the subdural space can be emptied after two or three taps, but if fluid persists after repeated taps over a period of weeks, operation for possible dissection of an underlying membrane, as in the case of subdural hematoma, may be required. Recovery is usually rapid and uneventful.

Although the cause of these effusions is unknown, the author speculates that in meningitis the arachnoid is damaged and allows the passage of a fluid rich in protein, which increases in volume by osmosis.

MADOW, Philadelphia.

Diseases of the Brain

PRIMARY MALIGNANT TUMORS OF THE NASOPHARYNX. R. M. GEIST JR., and U. V. PORTMANN, Am. J. Roentgenol. **68**:262 (Aug.) 1952.

Geist and Portmann review 72 consecutive cases of malignant tumors of the nasopharynx. During this time, a total of 325,000 new patients were seen at the clinic. Malignant tumors of the nasopharynx make up from 1 to 2% of the total number of malignant tumors. Grossly these tumors can be divided into three types: ulcerated, lobular, and exophytic. There has been disagreement on the histologic classification of tumors of the nasopharynx, particularly concerning the term lymphoepithelioma. Of the 72 malignant growths seen by the authors, the following histopathologic classification was made: transitional-cell carcinoma 21; squamous-cell carci-

noma, 19; lymphoepithelioma, 9; undifferentiated small-cell carcinoma, 4; adenocarcinoma, 1; basal-cell carcinoma, 1; lymphosarcoma, 6; reticulum-cell sarcoma, 1; fibrosarcoma, 1, and lipomyxosarcoma, 1. In eight cases pathologic classification was not possible, for various reasons.

One of the main reasons for the poor prognosis of malignant tumors of the nasopharynx is that most of the tumors are diagnosed relatively late in the course of the disease. Many of the tumors which are producing symptoms and signs sufficient to bring the patient to a doctor are missed by the physician until they are relatively far advanced. There are four general categories of presenting symptoms: auricular, respiratory, neurologic, and enlargement of cervical lympn nodes. The auricular symptoms result from obstruction of the Eustachian tube; the respiratory symptoms, from the presence of the tumor itself within the nasopharynx; the neurologic symptoms, from invasion of the base of the skull and pressure on the cranial nerves. Enlargement of the cervical lymph nodes represents metastasis. The first symptom in 15 of the 72 cases was neurologic. The tumors invade the bones of the base of the skull and grow through the foramen lacerum and the foramen ovale. After entering the middle cranial fossa, the growths usually remain extradural, producing compression of the cranial nerves. The fifth and sixth cranial nerves are most frequently involved, although the second, third, and fourth may also be implicated. The cranial nerves from the 9th to the 12th are located too far posteriorly to be involved intracranially, but they may be compressed or invaded by metastases in the retropharyngeal lymph nodes.

The most important procedure in establishing the correct diagnosis is a careful examination of the nasopharynx. Lateral and stereoscopic submentovertex roentgenograms of the skull are important to supplement the clinical examination in all cases.

X-irradiation is generally accepted as the only satisfactory form of treatment for malignant tumors of the nasopharynx. At the Cleveland Clinic deep x-ray therapy in the 200- to 250-kv. range is used, with a target-skin distance of 50 or 80 cm. The x-ray beam has a half-value layer of approximately 2 mm. cu. Two lateral and two maxillary portals are used in treatment. A skin dose of about 200 or 250 r is given daily until a tumor dose of about 4,000 r has been reached. Cervical metastases are treated by using large fields and irradiating to the limit of skin tolerance. In some cases the neck is treated even though enlarged lymph nodes cannot be felt. In far-advanced disease palliative x-ray therapy can be given for relief of pain. However, pain due to invasion of the base of the skull is seldom relieved.

Geist and Portmann have devised a method of staging the disease. Stage 1 is that in which the tumor is limited to the nasopharynx proper. In Stage 2 there may be palpable cervical lymph nodes but no other evidence extension or metastasis. Stage 3 includes any advance beyond the first two stages, specifically invasion of the skull. As might be expected, the prognosis is best for Stage 1 and worst for Stage 3. Thirteen patients in Stage 1 were treated, and three of them survived five years.

WEILAND, Grove City, Pa.

MORTALITY AND DISABILITY IN MULTIPLE SCLEROSIS: A STATISTICAL ESTIMATE OF PROGNOSIS. A. R. MACLEAN and J. BERKSON, J. A. M. A. **146**:1367 (Aug. 11) 1951.

One of the chief reasons for the inability to make a definitive judgment respecting the effect of any proposed therapeutic measure for multiple sclerosis is the lack of an adequately established estimate of prognosis which could be used as a basis on which to judge the results of treatment. It was with the idea of providing such a "control" that this study was undertaken.

To assure the minimum of a 10-year follow-up observation, the authors included only patients for whom a diagnosis of multiple sclerosis was made in 1939 or earlier. All patients were within the range of 15 to 45 years, inclusive, at the time of onset of the disease. All had exhibited the classic remissions and exacerbations and involvement of more than one portion of the nervous system. The authors' group comprised 518 patients meeting the above requirements.

The 10-year survival rate for this group of patients with multiple sclerosis was found to be 79%. This rate is about 85% of that for a normal population. Similarly, the five-year survival rate for the multiple sclerosis group was 93%, and this was 95% of the normal rate for this period.

The development of incapacitation could be studied, of course, only in those patients who were not already incapacitated at the time of the first visit. There were 278 patients on the basis of

whose data the rates of incapacitation were calculated. The 10-year survival rate for this group was 88%, as compared with 79% for the total group with multiple sclerosis. This reflected the fact that the present group, consisting only of patients who were working and walking when first seen, were, on the average, persons in whom the disease was not as malignant as in those who were incapacitated when first seen. At the end of five years, 96 of an original 100 were living, and 64 of these were able to work and walk. At the end of 10 years, 88 were living, and 42 of these were able to walk and work. Of the last figures, the persons living were 94% of the number in a normal group of similar age, and those walking and working represented 45% of the number expected to be living and well at the end of the 10-year period.

MacLean and Berkson point out that the rates obtained reflect a rather better outlook in respect to mortality and disability than is generally assumed for such patients, and that a five-year evaluation of results would appear to be the minimal period necessary for the deduction of reliable conclusions.

ALPERS, Philadelphia.

TOXIC ENCEPHALOPATHY OCCURRING DURING TOPICAL THERAPY WITH ASTEROL. J. W. WILSON, H. LEVITT, T. L. HARRIS, and E. M. HEILIGMAN, J. A. M. A. **150**:1002 (Nov. 8) 1952.

The authors describe two children in whom the use of Asterol (2-dimethylamino-6-[β-diethylaminoethoxy]-benzothiazole) caused encephalopathic toxicity. The first was a child of 4 years who was treated for a pruritic eruption of his trunk. Nine days after treatment was started there developed hallucinations and generalized muscle tremors, both tonic and clonic in type. There were no other positive neurological symptoms. Laboratory findings were not significant. The electrencephalographic pattern was not normal; neither did it constitute a definite abnormality.

All medication was stopped, and the tremors and hallucinations gradually cleared in six days. The skin lesion became worse, and after six days Asterol dihydrochloride tincture was again begun. After two days, disorientation and hallucinations recurred. Therapy was stopped, and all symptoms cleared after four days.

The second patient, an infant of 10 weeks, was treated with a 2.5% Asterol cream for lesions involving the trunk and extremities. On the 26th day of treatment, lethargy, followed by generalized convulsions, occurred. The electroencephalogram showed a paroxysmal tracing, but not of the type usually found in idiopathic epilepsy or in cerebral aplasia. Symptoms cleared after seven days.

In order that the occurrence of this alarming, but apparently reversible, neurotoxic reaction may be averted, the authors suggest that it is wise to avoid the use of this medicament with very young children, and they even caution against the frequent use of large quantities over extensive body surfaces in older children.

ALPERS, Philadelphia.

NEUROTOXIC SYMPTOMS FOLLOWING USE OF ASTEROL DIHYDROCHLORIDE. J. M. HITCH, J. A. M. A. **150**:1004 (Nov. 8) 1952.

Hitch describes three cases in which neuropsychiatric disorders developed after the use of tincture of Asterol dihydrochloride (2-dimethylamino-6-[β-diethylaminoethoxy]-benzothiazole dihydrochloride). The first patient was 2½ years old. The medicament was applied in enormous amounts and held in close apposition to the skin by an impervious dressing. Symptoms appeared after one week. The second patient was three years old, and the scalp lesion was inflamed and excoriated. The neuropsychiatric abnormalities did not appear till the 53d day. In both instances the symptoms appeared suddenly and consisted of muscular spasm, especially of the extremities, visual hallucinosis, and depression of the functions of the sensorium. Spontaneous recovery occurred a few days after treatment was stopped, and no recurrences or sequelae were observed.

The third patient, a boy of 4½ years, had previously had symptoms of psychogenic origin. After being under treatment for 11 weeks with Asterol dihydrochloride tincture for a scalp lesion, he had onset of dysarthria, muscular weakness and incoordination, and vomiting. While his symptoms cleared after cessation of medication, they recurred some five months later, accompanied by emotional difficulties. Symptoms here antedated the use of Asterol and persisted long after discontinuance of its use.

ALPERS, Philadelphia.

CONFIRMATION OF THE ROSENOW ANTIBODY-ANTIGEN SKIN REACTION IN IDIOPATHIC EPILEPSY. E. A. BERING, J. Neurol., Neurosurg. & Psychiat. **14**:205 (Aug.) 1951.

Rosenow has reported the isolation of an immunologically identifiable strain of α-Streptococcus from patients with idiopathic epilepsy. He also reports that the intradermal injection of antibodies specific for this strain elicits an erythematous skin reaction in patients harboring this organism, and in a high percentage of other epileptic patients as well. Bering presents an investigation and a statistical verification of this reaction in epileptic patients in England.

One hundred seventeen patients with idiopathic epilepsy and 105 nonepileptic patients were tested with an intradermal injection of antibodies made in the United States to strains of α-streptococci isolated from patients in the United States with various diseases, including idiopathic epilepsy.

The results of the tests, when submitted to statistical analysis, showed the incidence of positive reactions of the epileptic patients to the "epilepsy" antibody to be well beyond any chance variation.

Positive reactions to the "epilepsy" antibody occurred in 78% of the epilepsy patients and in 6.7% of the control patients. In the epileptic patients there was a definite correlation of negative reactions to the "epilepsy" antibody, normal electroencephalograms, and the time interval between the last seizure and the skin test.

All patients with a known organic cause of their seizures gave a negative reaction to the "epilepsy" antibody except two with post-traumatic epilepsy. A statistically higher incidence of positive reactions to the "epilepsy" antibody was found among nonepileptic persons living with epileptic patients than in the control group.

No evidence as to the relation of this reaction to the disease emerged from this study. The investigation was designed simply to verify the occurrence of the skin reaction as described by Rosenow, and no effort was made to study the etiological or pathological significance of the α-Streptococcus in the patients tested. However, Bering is of the opinion that the high incidence of positive reactions among people living with epilepic patients suggests a transmissible agent.

ALPERS, Philadelphia.

OLD CEREBRAL ABSCESS: RECURRENCE OF SYMPTOMS AFTER TWELVE YEARS. H. FELDMAN, Schweiz. Arch. Neurol. u. Psychiat. **66**:40, 1950.

On a hot, sunny day in August, 1937, a previously healthy man suddenly experienced headache and vertigo. His vision was disturbed the following morning, and, after falling from his bicycle, he was unable to get up because of paralysis involving the left arm and leg. The tendon reflexes were more active on the left side than on the right, but otherwise the hemiplegia was of the flaccid type. Left hemianesthesia was also observed. Lumbar puncture two hours after onset of hemiplegia was followed by a rapid return of power to the left arm and leg. The spinal fluid was under high pressure but was otherwise normal. The patient was in good health thereafter until March 9, 1949, when he received a blow to his abdomen. Four days later he experienced vertigo and paresthesias in the left lower limb. Rapidly progressive and ascending hemiplegia involving the left side came on the next day. Severe headache, projectile vomiting, and symptoms of meningitis with fever quickly ensued. A high count of polymorphonuclear leucocytes in the cerebrospinal fluid subsided after treatment with antibiotic drugs, but the general condition grew worse, and a large abscess deep in the right parietal lobe was evacuated. The patient died March 23.

Autopsy revealed a well-encapsulated abscess in the superior and internal portion of the centrum semiovale on the right side. This abscess had ruptured into the subarachnoid space on the medial surface of the posterior portion of the superior frontal gyrus; it communicated with a much larger, unencapsulated abscess in the parietal lobe. Cultures of pus obtained from the recent cerebral abscess and from one in the left faucial tonsil revealed a nonhemolytic Streptococcus. No evidence of a suppurative process was found elsewhere in the body.

DANIELS, Denver.

Diseases of the Spinal Cord

SPINAL TERATOMAS. D. FURTADO and V. MARQUES, J. Neuropath. & Exper. Neurol. **10**:384 (Oct.) 1951.

The spinal location of teratomas is a rare occurrence among the lesions causing compression of the spinal cord. The atypical features of the clinical course of spinal teratomas has been stressed in the literature. Mistakes in diagnosis are frequent, even in children. In adult subjects there is an additional cause of an atypical clinical picture, the not infrequent coexistence of teratoma and syringomyelia.

In the recorded cases of teratomas responsible for spinal cord compression, the tumors were found along almost any part of the spinal axis, though the terminal portion of the spinal column was a site of preference. Such tumors appear frequently in association with other, more or less recognizable, anomalies of somatic development, such as spina bifida and polydactyly. The presence of such anomalies should always raise suspicion as to the real cause of any observed compression of the spinal cord. The spinal teratomas are, like the intracranial teratomas, more frequent in children than in adults.

The teratomatous tumors, in general, are cystic, always containing hair, bone fragments, or cartilage in the neoplastic mass. The cyst is variable in size, white, and frequently contains fluid or an amorphous substance, which seems caseous. Histologically there is usually complete disorder. The tissues found are generally those derived from all three germinal layers, including skin fragments, nerve tissue, and muscle and osseous tissues.

The authors present an additional case, that of a woman of 42, with paraplegia, who gave a history of weakness of the lower extremities 20 years previously, followed by complete recovery; recurrence of the disease during pregnancy 17 years later, again followed by spontaneous recovery, and another exacerbation of symptoms, with complete paraplegia, in the course of another pregnancy. The spinal fluid and blood gave a strongly positive reaction for syphilis. A subarachnoid block, confirmed by manometric tests; the existence of a level of disturbance of superficial sensibility; the phenomena of automatism, and the paraplegia all pointed to the existence of compression of the spinal cord. The patient also had polydactyly.

She was given an intensive course of antisyphilitic treatment, which would serve to establish or exclude a syphilitic lesion of the spinal cord. Since the treatment did not prove of benefit, a myelographic examination was performed, and the level of compression was found to be at the fifth thoracic segment.

On operation at this level, a yellow-white tumor was found filling almost the whole of the dural space. The tumor was closely adherent to the spinal cord and could not be removed. When it was incised, caseous material, bone fragments, and hair were found.

In tracing the evolution of this patient's illness, it is probable that the first phase of her illness, in her 20's, was related to a stage of greater neoplastic activity, which then ceased, thus permitting functional restoration of the cord. Being a congenital tumor, the teratoma may have had phases of accelerated growth or edema, caused by the pregnancies, explaining the exacerbations.

The outlook for this patient is poor, as the nature of the lesion and its effect upon the cord hold out very little promise of benefit from surgical intervention. ALPERS, Philadelphia.

PROTRUDED LUMBAR INTERVERTEBRAL DISC: RESULTS FOLLOWING SURGICAL AND NON-SURGICAL THERAPY. B. M. SHINNERS and W. B. HAMBY, J. Neurosurg. **6**:450 (Nov.) 1949.

Shinners and Hamby sent questionnaires to 355 patients with protruded lumbar intervertebral disk who had been operated on and to 200 such patients who had not been operated on. Of the group which had undergone operation, 48.5% considered themselves cured and 39% benefited by operation, while only 29.5% of the group not operated on had recovered. More patients in both groups were working than admitted to being well. Of the group operated on, 91.5% were working, and of the group who had not received surgical treatment 85% were working. Simple removal of disk protrusions was done in 81% of the patients operated on. This was combined with or followed by spinal fusion in 19% of the cases. Simple removal of disk protrusions was

followed by definitely better results than removal combined with spinal fusion. Definitely better surgical results were obtained in private than in compensation patients. The private patient works in spite of, or adjusts his work to, some postoperative disability, but the compensation patient who admits that he is cured must expect to return to his original work, which may be too heavy for his back after operation.

J. A. M. A.

NEUROLOGIC MANIFESTATIONS FOLLOWING SPINAL ANESTHESIA. J. J. MICHELSON, Neurology **2**:255 (May-June) 1952.

Neurologic complications following spinal anesthesia vary greatly, with headaches, nausea, and vomiting, often associated with nuchal rigidity, rather common. Next in frequency is urinary retention. Among the more serious entities are spinal arachnoiditis, involvement of the cauda equina, and myelitis.

The question as to why complications develop has not been clearly answered. In some instances the causal agent is obvious, such as direct trauma or infection. In most cases the principal etiologic factor and/or mechanism of the damaging action of the anesthetic drug is rather obscure.

Lundy suggested that many spinal anesthesia accidents are due to factors other than the primary action of the anesthetic agent and that the spinal cord had probably been previously diseased if paralysis follows the use of ordinary doses of the anesthetic. Michelson, in a previous paper, emphasized the importance of a good history, neurologic examination, and, occasionally, cerebrospinal fluid analysis before the anesthetic is given, in order that serious neural damage may be prevented.

In this paper Michelson describes the neurologic manifestations following spinal anesthesia in four cases of intraspinal tumor.

At the time of injection of the anesthetic in these four cases an intraspinal space-taking lesion was present, though unrecognized. In all four cases the neurologic manifestations occurred soon after the operative procedure for which spinal anesthetic was used. The anesthetic agent was introduced in the usual amounts and solutions by an anesthetist of experience.

There was recovery, although incomplete, in two cases and none in the other two. Complete block of the cerebrospinal fluid was found in one case; a partial block only in the other three. In one case the site of obstruction was below the interspace at which the anesthetic was injected. In the other cases the lesion was above the level of injection.

Since the total protein level of the cerebrospinal fluid was elevated in all four cases, the question arises whether diffusion rate, local concentration, and/or toxicity of the drug is affected by an increased total protein concentration. If there were a relationship between increase of spinal fluid protein and toxicity of the anesthetic drug, determination of the total protein prior to injection of the anesthetic ought to become a routine procedure. Needless to say, a spinal anesthetic should never be injected in the presence of a cerebrospinal fluid block, because the obstruction interferes with the proper diffusion of the drug. Michelson proposes that the determination of the dynamics forms an essential part of each cerebrospinal fluid examination. Such an examination will prevent accidents associated with preexisting intraspinal pathology of the obstructing type. Cytologic analysis of the cerebrospinal fluid prior to the spinal anesthesia may well be another source of information.

All the above measures, in addition to a complete history and thorough physical and neurologic examinations, would be helpful in eliminating some of the complications of spinal anesthesia.

ALPERS, Philadelphia.

SEQUELS OF SPINAL ANESTHESIA. G. EVERBERG, Nord. med. **43**:64 (Jan. 13) 1950.

Replies to questionnaires sent to 771 patients after spinal anesthesia disclosed that 174 (22.2%) had various disturbances attributed to the anesthesia. Of the 93 patients with persisting complaints, 85 were reexamined. The results of the examinations compared with the results of diagnoses made on hospitalization subsequent to the spinal anesthesia or consultations with general practitioners or specialists suggest that in about one-third of the patients the complaints were attributable to factors other than the spinal anesthesia. Of 111 control patients given

hexobarbital (Evipal) anesthesia, 21 (18.9%) ascribed disorders to the anesthesia, and in almost half the patients the complaints persisted over a year, although hexobarbital anesthesia does not cause late neurologic complications. Everberg's investigations seem to show that full agreement as to the extent of protracted and intense discomfort after spinal anesthesia cannot be reached until a regular control study over a fairly long period is set up; such an investigation should be carried out as teamwork by the neurologist, psychiatrist, surgeon, and practitioner.

J. A. M. A.

Peripheral and Cranial Nerves

SPONTANEOUS COMPRESSION OF THE MEDIAN NERVE AT THE WRIST. G. S. PHALEN, J. A. M. A. **145**:1128 (April 14) 1951.

Phalen discusses pain and numbness in the hand in the area supplied by the median nerve. He points out that the median nerve may become compressed beneath the transverse carpal ligament without antecedent injury or disease. The exact pathogenesis of this spontaneous compression neuropathy has not yet been explained. The condition may be arrested or cured by simple section of the transverse carpal ligament.

Phalen has seen 11 such cases in a period of two years. In this group, 10 hands of eight patients were operated upon. In four hands a neuroma of the median nerve was encountered just proximal to the transverse carpal ligament; in the other six hands it was felt that the slight flattening and enlargement of the median nerve as it passed beneath the transverse carpal ligament was within normal limits. In two hands of two patients there appeared to be some increase in the normal amount of connective tissue about the median nerve. The results of operation in all cases were uniformly good.

Only a few cases of the syndrome have been reported. Phalen feels that if the physician keeps the syndrome in mind when he is confronted with a patient complaining of pain and numbness in the median distribution in the hand, the diagnosis will be made in many cases.

ALPERS, Philadelphia.

TUMOR OF THE GLOMUS JUGULARE WITH EXTENSION INTO THE MIDDLE EAR (NON-CHROMAFFIN PARAGANGLIOMA OR CAROTID-BODY-TYPE TUMOR). E. ALEXANDER, P. R. BEAMER, and J. O. WILLIAMS, J. Neurosurg. **8**:515 (Sept.) 1951.

Most tumors of the glomus jugulare now recorded in the literature were discovered because of signs and symptoms related to the ear; usually these were deafness and chronic otorrhea; occasionally they were complaints of dizziness, tinnitus, and pain.

This tumor is encountered most frequently in the age group of 30 to 50 years. In the relatively small number of cases (28) thus far recorded in the literature, there is a higher incidence (22) among women. The medical history is usually one of relatively long duration, and in at least two cases the patients had symptoms for 20 years or more.

The tumor is histologically similar to the carotid-body tumor and to the rare tumor occurring in the region of the aortic arch. Tumors of this type are locally invasive but are usually benign and very slow in their growth. Occasionally such a tumor can be removed completely when discovered in the early stages.

There have been at least seven deaths among the recorded cases: Two patients died after the attempted removal of the tumor; four died apparently of gross extension of the tumor into the intracranial cavity, and one died of meningitis and a cerebellar abscess.

The authors report a case of tumor of the glomus jugulare (verified by biopsy) occurring in a woman aged 35 who gave a history of poor health for three years, deafness and tinnitus in the left ear associated with ataxia for one year, paralysis and numbness of the left side of the face, voice change for four months, and hiccup for one month.

Neurologic examinaiton showed no abnormalities of the first six cranial nerves. There were complete peripheral paralysis of the left 7th nerve, with only faint motion of the orbicularis oris on the left, and complete paralysis of the 8th, 9th, 10th, 11th, and 12th cranial nerves on the left. The drum membrane of the left ear showed, protruding through it, a smooth, red mass

with very slight pulsations synchronous with the heart beat. There were ataxia of the left arm and leg, hyperactive deep reflexes on the left, an unsustained ankle clonis of the left foot, and a questionable Babinski sign on the left.

Angiography of the left common carotid artery showed a normal vascular pattern for the anterior and middle cerebral vessels and a very vascular mass which filled the floor of the posterior fossa on the left side, extending slightly across the midline. It extended posteriorly as far as the foramen magnum and seemed to extend into the middle fossa as well.

Because of the extreme vascularity of this tumor and its extensive nature, with invasion of bone and obvious growth across the midline, it was felt to be inoperable. The patient was subjected to extensive radiation therapy and showed definite improvement, but the outlook is not considered good. It remains to be seen whether roentgen therapy will be effective in shrinking a tumor of this type.

ALPERS, Philadelphia.

Treatment, Neurosurgery

USE OF CURARE IN TREATMENT OF ANTERIOR POLIOMYELITIS. A. G. BOWER, O. L. HUDDLESTON, and D. HOVSEPIAN, Am. J. Med. **8**:160 (Feb.) 1950.

The treatment employed by Bower and associates consisted in administering curare in the form of purified Chondodendron tomentosum extract (Intocostrin) in doses of 0.9 to 1.5 units per kilogram of body weight two or three times daily. Physical therapy consisted in passive stretching combined with or followed by active assistive exercises for 20 to 40 minutes after each injection. The effect of the drug and physical therapy was observed on 40 patients. Response to this therapy was most satisfactory when treatment was begun within two to six days after the onset of muscle involvement. Patients showing a combination of severe muscle tightness and weakness were less likely to be benefited by curare than those showing muscle tightness alone. Patients with extensive paralysis and weakness were not greatly benefited by the curare therapy. Localized pain, tenderness, and soreness of the soft tissues in and about the joints were observed in six patients, but insufficient data are available to permit one to state definitely that these symptoms were caused by purified Chondodendron tomentosum extract injections. The muscular tightness of some patients who were refractory to pack therapy was relieved by the drug and physical therapy. A few patients were refractory to either hot packs or curare therapy, as well as to a combination of the two. Curare was helpful in treating some patients who had to be placed in the respirator. Of the 10 patients who received curare during treatment in the respirator, 4 made a satisfactory recovery. The drug was most valuable in the early phases of the disease in patients who were not coordinating their breathing with the respirator. It stopped aberrant irregular impulses from coming through to the intercostal muscles and diaphragm, and the patient's breathing assumed the rhythm of the respirator. Relief of laryngeal and intercostal tightness by purified Chondodendron tomentosum extract saved at least one patient, and possibly two more, from asphyxiation.

J. A. M. A.

News and Comment

AMERICAN LEAGUE AGAINST EPILEPSY

Jerry Price Memorial prizes for dissertations in epilepsy, with a total value of $1,000, were awarded at the annual meeting of the American League Against Epilepsy, held in Boston, Aug. 22, 1953. Essayists were medical students.

Cash prizes went to Dominick P. Purpura, Harvard Medical School; Arnold M. Sobel, New York University College of Medicine; William C. Brown, University of Utah College of Medicine; and J. W. A. Terrell, University of Texas School of Medicine. Twenty-three other contestants received prizes of books or of subscriptions to *Epilepsia*.

Books

Cerebral Changes Following Electrically Induced Convulsions: An Experimental Study on Cats. By Hans Hartelius. Acta psychiatrica et neurologica scandinavica, Supplement 77. Price, 20 Swedish crowns. Pp. 128, with 24 illustrations. Ejnar Munksgaard Forlag, Nørregade 6, Copenhagen, 1952.

Studies published by previous authors have been contradictory as to the changes in the brain following electric shock; so the author has reviewed the literature and undertaken a controlled investigation, using cats and preparing the material with rigorous precautions against accepting artifacts and incidental findings. The fact that he made no mistakes when separating those animals who had undergone electrically induced convulsions from those who had received none is a credit to the perspicacity of the investigator. And yet the changes, such as they are, are not of a kind to meet the wandering or inattentive eye. Some sections were insufficiently demonstrative, while others were misleading, so that a number of slides had to be seen and then reviewed, new ones cut and stained, and, finally, when the changes were well fixed in the mind of the investigator, the sections examined a third time "blind," and even a fourth time, in order to permit the utmost concordance. Finally, the statistical work to prove the validity of the findings had to be calculated, with the result that the final opinion of the investigator could be stated with less than a chance in a thousand of the opinion being due to chance. This is a deliberate and intricate work, and will prove to anyone's satisfaction that there are histologic changes produced in the brain of cats by application of the electric current in a manner analogous to that of electroshock therapy in man. Future arguments may take place over the severity and significance of these changes, but there can be no doubt that they have been demonstrated.

The author points out that after repeated electroshocks there are dilated perivascular spaces of irregular shape in which scattered histiocytic elements are sometimes present; that occasionally free pigment, but oftener phagocytosed, is found in these spaces. Glia cells are increased in the parenchyma, particularly in the neighborhood of ganglion cells. "Satellitosis appeared to be a relatively specific phenomenon . . . Sporadic cases of true neuronophagia also belonged to the category of glia reactions." As far as changes in the nerve cells are concerned (and here the technical part of the monograph recommends chromalum-gallocyanin after fixation in Carnoy's solution), the author is more concerned with morphology. "It appeared easier to record a greater chromaffinity from nerve cell to nerve cell than to grade the chromaffinity in general of the nerve population. A special phenomenon found in certain pyramidal cells, i. e. nuclear hyperchromatism with coincident relative chromophobia in the cytoplasm, particularly in its periphery, also seemed to be of great value in substantiating the diagnosis 'shocked'. Particular note was made of focal accumulations of such cells and of a greater variability of nerve-cell chromaffinity in circumscribed areas." Concerning minute hemorrhages, the author

found them more frequently in the shocked than in the nonshocked animals, yet they were always terminal and not of an age that would suggest their occurrence at the time the shocks were administered. "The most plausible explanation appears to be that the electric shocks, in combination with some individual factor, resulted in an increased tendency to terminal cerebral hemorrhages."

There is an interesting table recording the methods and results of 15 investigations. There are 22 columns. The photomicrographs are rather pale, in contrast to those obtained with aniline dyes, but thoroughly readable. The author has made his point.

Parkinson's Disease and Its Surgical Treatment. By Leslie G. Oliver, M.R.C.S. Eng.; L.R.C.P. London. Price, 12s. 6d. Pp. 96, with 12 illustrations. H. K. Lewis & Co., Ltd., 136 Gower St., London W.C. 1, 1953.

"There is at present no cure for Parkinson's disease, but in a small proportion of cases substantial improvement may be accomplished by surgery if great care is taken in the selection of patients. This account has been written chiefly to dispel exaggerated claims for surgery, but also at the same time to counteract prejudice, which tends to deprive some patients of relief from a most distressing malady."

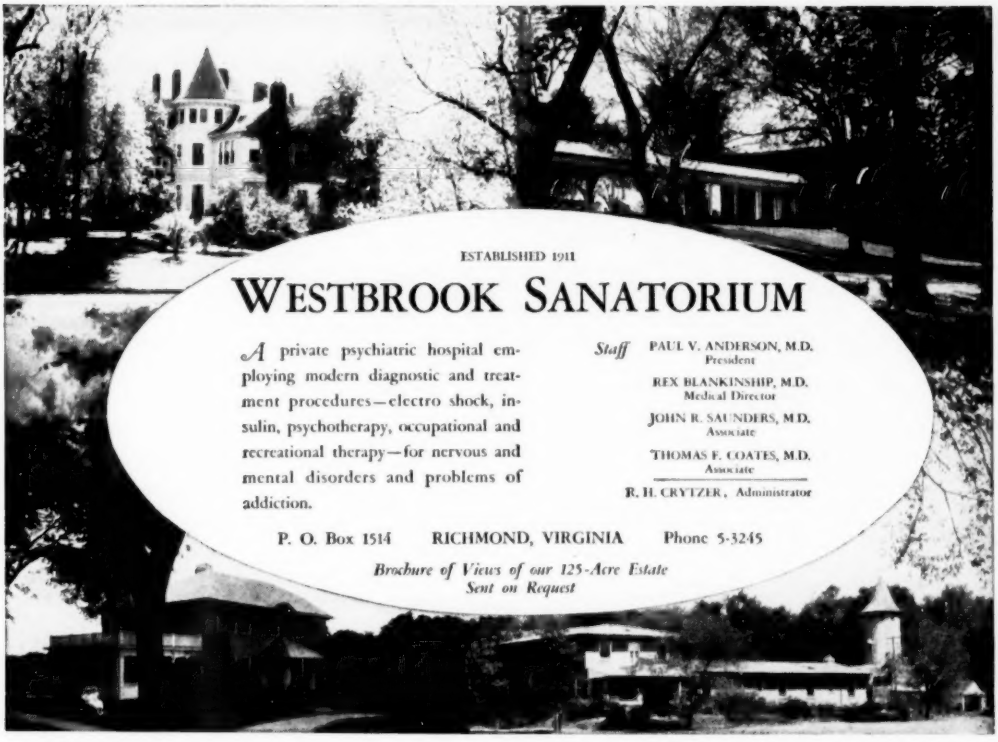
The author has performed spinal pyramidotomy in 40 cases, performing a bilateral operation in 25 of them. The results were poor. He prefers a more radical operation, namely, complete section of the lateral column, which he has carried out in 14 cases, without a death and with uniformly satisfactory improvement. The complications have been similar to those seen after spinothalamic chordotomy, in addition with considerable loss of strength, usually temporary, in the homolateral extremity. The cortical and subcortical operations are frowned upon.

The Living Brain. By W. Grey Walter. Price, $3.95. Pp. 311. W. W. Norton & Company, Inc., 101 5th Ave., New York 3, 1953.

This book is evidently written for the educated general reader, and not for the trained specialist. It begins with a sketch of the evolution of the nervous system that is remarkably well done. It is then pointed out that man was very slow in recognizing the functions of the brain, not realizing that it is the organ that makes him superior to all other animals. Walter then emphasizes the recent rapid development in the understanding of how the brain works through electroencephalography and suggests that at last we may be seeing the physical counterparts of mental events. The recently devised techniques related to electroencephalography have provided new knowledge that has practical application to epilepsy and hallucinations. He describes the possibility that the brain may work as a scanning mechanism and explains the working models that have been made by the physicists. Berger's discovery of the electroencephalograph and Pavlov's quantitative studies of conditioned reflexes are considered to be the two important paths that have converged to give our present understanding of the process of learning. Walter considers the scanning theory as the climax of recent research which gives us a possible way to explain the learning process. In this connection he describes a marvelous model made by himself which behaves almost like a live tortoise.

His theories are well explained and make interesting reading. One of his main points is that the brain is characterized by being unique for each individual man. It allows for much idiosyncrasy. The other organs of the body are practically uniform and allow for very little idiosyncrasy. Thus the brain is essentially the organ of personality.

This book is a stimulating one for the neurologist and psychiatrist, but for the general reader it is dangerous, because the author does not make it clear as to when he is discussing facts and when he is merely speculating. The style is sprightly but provocative and at times bumptious. It is to be deplored that an investigator with so much originality and ability has so thrown off scientific restraints that he at times is fantastic.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